Janssen Research & Development *

Clinical Protocol

A Phase 2, Open-label, Single-arm, Multicenter Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Efficacy of Switching to RPV Plus Other ARVs in HIV-1-infected Children (Aged 2 to <12 years) who are Virologically Suppressed

Protocol TMC278HTX2002; Phase 2
AMENDMENT 3

TMC278 (rilpivirine)

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	This document
Amendment 2	18 December 2019
Amendment 1	24 April 2019
Original Protocol	14 Jan 2019

Amendment 3 (this document)

Overall Rationale for the Amendment: this amendment is created to include an optional intensive PK substudy at several study sites and to clarify some of the inclusion and exclusion criteria.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design	It has been added that, at some sites, an optional PK substudy may be performed to collect intensive PK data in children ≥6 years with body weight ≥25 kg on the day of intensive PK (substudy), which will require additional assessments as specified in the substudy protocol.	The PK data of the substudy will be used in support of the refinement of a population PK model across age groups to gain a better understanding of PK profiles for participants included in the study.
1.1 Synopsis 1.2 Schema 4.1 Overall Design 4.3 Justification for Dose 6.1 Study Interventions Administered 6.6.2 Dose Modification (Adjustment) Rules 9.5 Independent Data Monitoring Committee Analyses	The RPV dose for participants with a body weight <20 kg was amended from 15 mg to 12.5 mg once daily.	The RPV dose was amended based on data from the first mini-cohort of 5 children with a body weight <25 kg in the study. This was endorsed by the IDMC.
6.6.2 Dose Modification (Adjustment) Rules	Details were added for a switch to the 12.5-mg dose in participants <20 kg. It was specified that the RPV dose could change based on further analysis and IDMC recommendations.	To allow for flexibility in case of changes based on further analysis and IDMC recommendations.
5.1 Inclusion Criteria and throughout the document	The minimum body weight for enrollment in the study was adjusted from 11 to 10 kg.	To align with the WHO weight bands for ARV dosing in children.
1.3.1 General Schedule of Activities 5.2 Exclusion Criteria 5.4 Screen Failures	It has been clarified that retesting of an ECG leading to exclusion will be allowed once at screening.	To align with the allowed retesting for laboratory abnormalities at screening.
5.2 Exclusion Criteria	It was specified that delays in QRS duration >90 ms were allowed if there are no other conduction abnormalities present.	Clarification.
4.3 Justification for Dose	Text on the standard allometric scaling factor of 0.75 was deleted.	The allometric scaling factor was adjusted based on emerging PK data.

Section number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 General Schedule of Activities 2.3.5 Overall Benefit/Risk Assessment 4.1 Overall Design 4.2 Scientific Rationale for Study Design 8.2.1 Physical Examination 8.2.4 Clinical Safety Laboratory Assessments 10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV 10.7 Appendix 7: Clinical Laboratory Tests	It has been clarified that endocrine assessments, adrenocorticotropic hormone stimulation testing, and Tanner staging are to be performed for all participants aged ≥6 to <12 years (including participants who turn 12 years old during the study).	To ensure that these assessments continue to be performed in participants turning 12 years old during the study.
1.1 Synopsis 1.2 Schema 1.3.2 Schedule of Activities for Intensive Pharmacokinetic Sampling 1.3.3 Schedule of Activities for Switch to Adjusted RPV Dose (if Applicable) 4.1 Overall Design 6.1 Study Interventions Administered	It has been clarified that the intensive PK assessment can be done 2 weeks and 4 weeks after RPV treatment with the adjusted dose, instead of after at least 2 weeks and at least 4 weeks since the time window is specified in Section 8.	To correct for the discrepancy between sections.
1.1 Synopsis 8.5.3 Pharmacokinetic Parameters and Evaluations	Plasma concentration at 24 hours postdose was added to the PK parameters.	PK parameter added for completeness.
1.3.1 General Schedule of Activities 1.3.3 Schedule of Activities for Switch to Adjusted RPV Dose (if Applicable) 4.1 Overall Design	It was added that sampling for endocrine assessments and ECGs are also to be done at follow-up visit.	To clarify that at the follow-up visit any abnormal assessment can be retested, including endocrine assessments and ECGs.
10.4 Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Spermicides or spermicide-containing contraceptives were deleted from the list of contraceptives that could not be used as a sole method of contraception during the study.	Spermicides are not to be used as contraceptives as this could potentially increase the rate of HIV-1 transmission.
5.4 Screen Failures	It was specified that one additional rescreening is allowed in case inclusion and exclusion criteria are updated.	To allow for flexibility in case of updates to the criteria.
6.1 Study Interventions Administered	It has been added that the content of the standard breakfast is to be recorded in the CRF.	Breakfast details will be collected in order to interpret the pharmacokinetic data as needed.
6.6.2 Dose Modification (Adjustment) Rules	It has been clarified that dose adjustments following weight loss are only needed upon confirmation of the change in weight.	To ensure that no dose adjustments are made before confirmation that the weight loss is not due to an underlying condition.

Section number and Name	Description of Change	Brief Rationale
8.2.2 Vital Signs	The 5 minutes of rest in a quiet setting prior to the vital sign measurements were removed from the protocol.	The 5 minutes of rest prior the vital sign measurements are not clinically important for children.
10.1 Appendix 1: Abbreviations and Trademarks	The definition of virologic response was removed.	The definition of virologic response was removed for clarification reasons as it was not in line with inclusion criterion 4.1 (virologically suppressed with documented evidence of at least 2 plasma viral loads <50 HIV-1 RNA copies/mL), nor with the international guidelines considering virologic response as confirmed plasma viral load <50 HIV-1RNA copies/mL. Since both virologic thresholds of <50 and ≥50 copies/mL and <400 and ≥400 copies/mL will be used in the analysis (as defined in Section 3, Objectives and Endpoints), the Sponsor acknowledged that the definition of virologic response in Section 10.1 could be considered potentially misleading.
10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV	Roxithromycim was added to the list of drugs with established and theoretical drug interactions with commonly used comedications and RPV.	To align with Section 6.5.3.
10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV	It was specified that glucocorticoids were only disallowed if taken chronically.	To align with Section 6.5.3.
Throughout the document	Some administrative and editorial adjustments were made.	Clarification.

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1 PROTOCOL SUMMARY

1.1 Synopsis

A Phase 2, Open-label, Single-arm, Multicenter Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Efficacy of Switching to RPV Plus Other ARVs in HIV-1-infected Children (Aged 2 to <12 years) who are Virologically Suppressed.

Each participant must have a body weight of at least 10 kg (ie, the 10th percentile of the growth curve for body weight for healthy girls aged 2 years), be virologically suppressed (ie, human immunodeficiency virus [HIV]-1 ribonucleic acid [RNA] <50 copies/mL) on a stable antiretroviral (ARV) regimen for at least 6 months at screening, and have no history of virologic failure. The participants should also lack any rilpivirine (RPV) resistance-associated mutations (RAMs) as evidenced by their historical HIV-1 genotyping results, if available. Participants aged ≥2 to <6 years, however, are required to have historical HIV-1 genotyping results available at screening, to be provided to the sponsor. The availability of the historical HIV-1 genotyping results and the subtype need to be recorded in the CRF.

Rilpivirine (formerly known as TMC278 [R278474]), a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type (WT) HIV-1 and against NNRTI-resistant HIV-1 mutants. Rilpivirine as an oral formulation offers the convenience of once-daily dosing with potent antiviral activity and has a favorable safety and tolerability profile in adults and adolescents.

Rilpivirine at a dose of 25 mg once daily (qd) has been approved for treatment of ARV treatment-naïve HIV-1-infected adults in multiple countries, including the United States, Canada, Japan, and countries in the European Union, either as a single-agent 25-mg tablet (EDURANT) or as part of several fixed-dose combinations (ie, with the integrase inhibitor dolutegravir [DTG], with tenofovir disoproxil fumarate/emtricitabine [TDF/FTC], and with tenofovir alafenamide/FTC [TAF/FTC]). In most countries, including the United States and countries in the European Union, the indication of EDURANT is restricted to patients with a plasma viral load ≤100,000 HIV-1 RNA copies/mL. In several countries, including the United States and countries in the European Union, this indication has been extended to the pediatric population (ie, adolescents aged ≥12 to <18 years). The further pediatric development of RPV is ongoing.

OBJECTIVES AND ENDPOINTS

Objectives

Primary Objectives

- To evaluate the steady-state pharmacokinetics (PK) of RPV and determine the appropriate dose of RPV in combination with other ARVs in participants aged ≥2 to <12 years with a body weight of <25 kg.
- To evaluate the safety and tolerability of RPV in combination with other ARVs in participants aged ≥2 to <12 years over a 24-week treatment period.

Secondary Objectives

- To evaluate the safety and tolerability of RPV in combination with other ARVs over a 48-week treatment period.
- To evaluate the efficacy of RPV in combination with other ARVs over a 24- and 48-week treatment period.
- To evaluate population PK and PK/pharmacodynamic (PD) relationships for safety and efficacy of RPV in combination with other ARVs.

- To assess resistance in case of loss of virologic response to RPV in combination with other ARVs.
- To evaluate treatment adherence to RPV in combination with other ARVs over a 24- and 48-week treatment period.

Exploratory Objectives

- To assess the palatability of the 2.5-mg tablet formulation of RPV, if applicable.
- To assess the swallowability of the 25-mg tablet formulation of RPV, if applicable.
- To assess archived viral resistance, if feasible depending on available blood volume.

Endpoints

Primary Endpoints

- Area under the plasma concentration-time curve from time of administration up to 24 hours postdose of RPV, as derived from the intensive PK assessments.
- Incidence of grade 3/4 adverse events (AEs), serious adverse events (SAEs), HIV-related events (including acquired immune deficiency syndrome [AIDS]-defining illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection), and AEs leading to discontinuation of study intervention through 24 weeks of study treatment.

Secondary Endpoints

- Incidence and severity of AEs/HIV-related events and their relatedness to RPV through 24 and 48 weeks of study treatment.
- Change from baseline over time and shift in toxicity grades/abnormalities versus reference for clinical laboratory parameters, electrocardiogram (ECG) parameters, vital signs, and physical examination through 24 and 48 weeks of study treatment.
- Proportion of participants with HIV-1 RNA <50 and ≥50 copies/mL using the Food and Drug Administration (FDA) Snapshot approach through 24 and 48 weeks of study treatment.
- Proportion of participants with HIV-1 RNA <400 and ≥400 copies/mL using the FDA Snapshot approach through 24 and 48 weeks of study treatment.
- Immunologic changes, measured by cluster of differentiation (CD)4^+ cell count (absolute and percentage relative to total lymphocytes), through 24 and 48 weeks of study treatment.
- Pharmacokinetic parameters of RPV (other than area under the plasma concentration-time curve [AUC]), as derived from the intensive PK assessments.
- Pharmacokinetic parameters of RPV, as derived by population PK modeling, through 24 and 48 weeks of study treatment.
- Viral genotype at the time of virologic failure through 24 and 48 weeks of study treatment.
- Treatment adherence, as assessed by the Pediatric European Network for the Treatment of AIDS (PENTA) adherence questionnaire and by study intervention accountability, through 24 and 48 weeks of study treatment.

Exploratory Endpoints

- Responses to the palatability questionnaire after 2 weeks of study treatment.
- Responses to the swallowability questionnaire after 2 weeks of study treatment.
- Mutations in HIV-1 deoxyribonucleic acid (DNA) or in HIV-1 RNA, as assessed by retrospective peripheral blood mononuclear cell (PBMC)- or plasma-based analyses, through 24 and 48 weeks of study treatment.

Hypothesis

No formal hypothesis will be tested.

OVERALL DESIGN

This is a Phase 2, open-label, single-arm, multicenter, interventional study in HIV-1-infected participants (boys and girls) aged ≥2 to <12 years with a body weight of at least 10 kg to evaluate the PK, safety, tolerability, and efficacy of switching to RPV once daily in combination with other, investigator-selected ARVs.

All participants will have a screening phase aimed to be completed within 6 weeks. However, the screening phase can be prolonged with maximum 2 weeks in case of unforeseeable circumstances. All participants will receive open-label treatment for 48 weeks in the study intervention phase. Upon study completion, participants who continue to experience clinical benefit from treatment with RPV will be offered the opportunity to continue study treatment in the pediatric rollover study TMC278IFD3004. The total study duration for each participant, including screening and study intervention phases, will be approximately 54 weeks. Participants who do not roll over in the pediatric study TMC278IFD3004, who withdraw from the study on or before the Week 48 visit (unless consent/assent is withdrawn), who have ongoing (S)AEs at the last study visit, or who need retesting of abnormal laboratory results, abnormal ECG, cortisol-related retesting, or plasma viral load/resistance testing at the last study visit will have a follow-up visit 4 weeks after their last study visit.

The end of study is considered as the last visit for the last participant in the study.

At some sites, an optional PK substudy may be performed to collect intensive PK data in children ≥6 years with body weight ≥25 kg on the day of intensive PK (substudy), which would require additional assessments as specified in the substudy protocol.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study. The IDMC will be the same committee as for the study TMC278-TiDP38-C213 (C213).

NUMBER OF PARTICIPANTS

To comply with overall regulatory requirements, approximately 40 participants (including at least 12 participants with a body weight of <25 kg at baseline) will be enrolled in this study and in Cohort 2 (participants aged ≥6 to <12 years) of the ongoing study C213 combined. A target of approximately 25 to 30 participants will be enrolled in this study. The actual number of participants in this study will depend on the number of participants enrolled in Cohort 2 of study C213.

INTERVENTION GROUPS AND DURATION

At the time of Amendment 2 writing, the RPV dose recommendations of 25 mg and 15 mg for participants with a body weight ≥25 kg and <25 kg, respectively, were determined based on accumulating data and were endorsed by the IDMC, in order to achieve a similar exposure to RPV compared to adults. **At the time of Amendment 3** writing, the dose for participants <20 kg was amended to 12.5 mg, based on data from the first mini-cohort of 5 children with a body weight <25 kg in the study, and was endorsed by the IDMC.

- RPV 25 mg qd for participants with a body weight of ≥25 kg
- RPV 15 mg qd for participants with a body weight of ≥20 and <25 kg.
- RPV 12.5 mg qd for participants with a body weight of ≥10 and <20 kg.

Appropriateness of these doses will be further evaluated as per instructions in the body of the protocol.

Rilpivirine (25 mg, 15 mg, 12.5 mg, or another adjusted weight-based dose) will be orally administered once daily in combination with an investigator-selected background regimen containing other ARVs such as nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) and integrase inhibitors. Protease inhibitors and ARVs requiring a PK booster, however, are disallowed from baseline onwards.

In participants with a body weight of <25 kg, an intensive PK assessment will be performed after 4 weeks of study treatment to evaluate the appropriateness of their RPV dose. If the RPV dose needs to be adjusted, an additional intensive PK assessment will be performed after 2 weeks of treatment with the adjusted RPV dose to evaluate the dose modification.

Overall across studies TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥10 kg) and C213 (Cohort 2; children aged ≥6 to <12 years), approximately 40 participants will be enrolled of which at least 12 participants with a body weight of <25 kg at baseline, including at least 7 participants with a body weight of <20 kg at baseline. To accommodate overall regulatory requirements concerning the evaluation of RPV in the pediatric population, the intensive PK data from this study TMC278HTX2002 will be combined with the data from study C213 Cohort 2 as available.

The decision to modify the RPV dose for a specific group of participants will be made by the sponsor upon IDMC recommendation. CCI [redacted]

The participants will continue the study intervention and ARV background regimen (through the data review periods, if applicable) until they all reach a total treatment duration of 48 weeks (or discontinue earlier). Dose adjustments of RPV due to changes in body weight, if applicable, are allowed.

EFFICACY EVALUATIONS

Key efficacy assessments include determination of plasma HIV-1 RNA viral load and measurement of CD4+ cell count.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic parameters will be derived from the intensive PK assessments performed in participants with a body weight of <25 kg. CCI [redacted]

Intensive Pharmacokinetics

Based on the individual plasma concentration-time data, using the actual dose taken and the actual PK sampling times, the following PK parameters of RPV will be derived:

C_{0h}, C_{24h}, C_{min}, C_{max}, $C_{ss,av}$, t_{max}, AUC_{24h}, CL/F, V_{ss}/F, and FI

CCI [redacted]

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Pharmacokinetic/PD evaluations will be performed to explore the relationship between PK and safety/efficacy variables.

SAFETY EVALUATIONS

Key safety assessments will include the monitoring of (S)AEs and HIV-related events (including AIDS-defining illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection [cut-off for Stage-3 illnesses is 6 years of age per criteria from 2014]), clinical laboratory tests (including endocrine assessments in participants aged ≥6 to <12 years, including participants who turn 12 years old during the study), cardiovascular safety monitoring (vital signs and 12-lead ECGs), and physical examination (including growth). In addition, an evaluation of depression will be performed using questionnaires or other means (as available at the site) as part of local standard of care for this population.

OTHER EVALUATIONS

Other assessments and procedures include resistance testing through HIV-1 genotyping and a retrospective evaluation of RAMs in PBMCs, documenting RPV intake through diary completion (only for participants scheduled for an intensive PK visit), treatment adherence, and palatability and swallowability assessments.

STATISTICAL METHODS

The primary analysis (with formal database lock) will be done when all participants have reached Week 24 (or discontinued earlier). The final analysis (with formal database lock) will be done when all participants have reached Week 48 (or discontinued earlier). A detailed Statistical Analysis Plan (SAP) for each analysis will be written and signed off prior to database lock.

Sample Size Calculation

No formal sample size calculation was performed. The sample size is based on overall regulatory requirements and the number of participants enrolled in Cohort 2 in study C213.

Efficacy Analysis

Plasma Viral Load

An outcome analysis (ie, proportion of participants with a plasma viral load <50 and <400 HIV-1 RNA copies/mL) will be performed using Snapshot approach. The Snapshot analysis is based on the last observed plasma viral load data within the visit window (ie, Weeks 24 and 48). The proportion of participants with virologic failure (ie, HIV-1 RNA ≥50 and ≥400 copies/mL) per Snapshot approach will be provided. Participants who switched ARVs for tolerability reasons not allowed per protocol will be considered as virologic failures for this Snapshot approach. Proportions will be expressed as percentages with Clopper Pearson 95% confidence interval (CI) at each time point. at each time point.

$CD4^+$ Cell Count

The analysis will be based on observed values and on imputed values using NC=F, ie, participants who prematurely discontinued the study will have their $CD4^+$ cell count following discontinuation imputed with the baseline value (resulting in a change of 0), and will have last-observation-carried-forward imputation for intermediate missing values.

Actual values and changes from baseline will be descriptively and graphically presented.

Safety Analysis

Adverse Events/HIV-related Events

For each treatment-emergent AE/HIV-related event, the percentage of participants who experience at least 1 occurrence of the given event will be tabulated per study phase (ie, screening phase, intervention phase, and follow-up). Separate tabulations will be made by severity and relationship to the study intervention, as appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study intervention due to an AE, or who experience a grade 3/4 AE, an AE of special interest, or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Descriptive statistics include number of observations (n), mean, standard deviation (SD), median, minimum, and maximum.

Frequency tabulations of the changes from baseline will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). For the tests available, laboratory abnormalities will be determined using the Division of AIDS (DAIDS) grading table. Frequency tabulations of worst abnormality grade after baseline will be generated. As appropriate, frequency tabulations and listings will be provided for participants who develop a grade 3/4 laboratory abnormality.

Electrocardiogram

Descriptive statistics of ECG values and changes from baseline will be summarized at each scheduled time point. Descriptive statistics include number of observations (n), mean, SD, median, minimum, and maximum. Frequency tabulations of the abnormalities will be made.

Vital Signs

Descriptive statistics of pulse rate and blood pressure (systolic and diastolic) (supine and standing) values and changes from baseline will be summarized at each scheduled time point. Descriptive statistics include number of observations (n), mean, SD, median, minimum, and maximum. The percentage of participants with values beyond clinically important limits will be summarized at each time point.

Physical Examination

Physical examination findings will be summarized at each scheduled time point per body system. Physical examination abnormalities will be listed.

Growth will be followed regularly and evaluated consistently using standardized growth charts. Descriptive statistics of height, height-for-age, weight, weight-for-age, body mass index (BMI), and BMI-for-age will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Descriptive statistics include number of observations (n), mean, SD, median, minimum, and maximum.

Tanner stage (for pubic hair and genitalia/breasts) will be cross-tabulated versus baseline by age. 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.

Pharmacokinetic Analysis

Descriptive statistics, including sample size (n), arithmetic mean, SD, (percentage of) coefficient of variation ([%]CV), geometric mean, median, minimum, and maximum, will be calculated for all individual derived PK parameters of RPV.

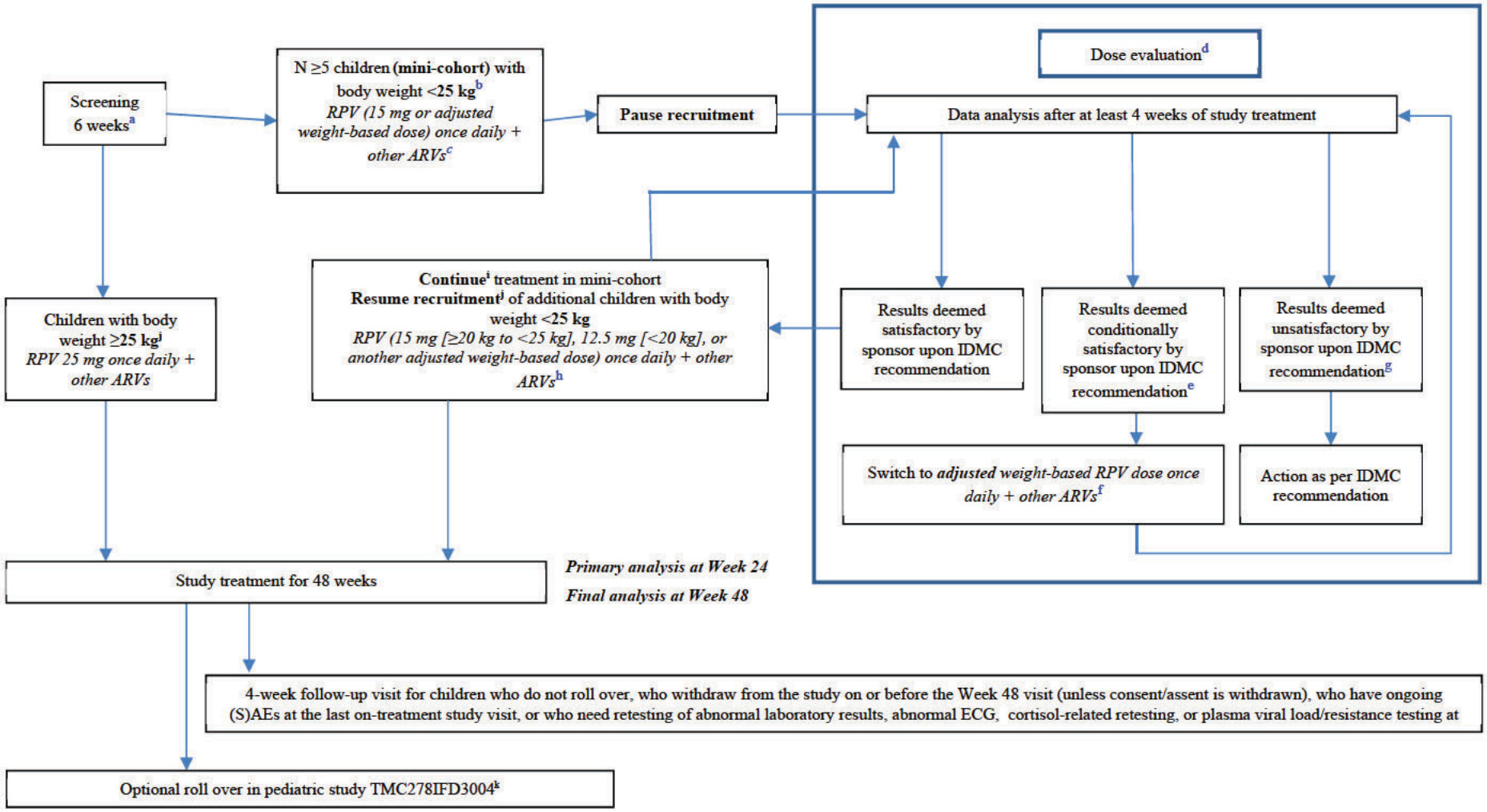
Efficacy and safety parameters will be subjected to a PK/PD analysis. CCI [redacted]

Other Analyses

Frequency tabulations and listings will be generated.

1.2 Schema

Figure 1: Schematic Overview of the Study



a The screening phase can be prolonged with maximum 2 weeks in case of unforeseeable circumstances resulting in a maximum screening phase duration of 8 weeks.
b In the current study and study C213 combined.
c Intensive PK assessment after 4 weeks of study treatment.
d The appropriateness of the RPV dose will be assessed.
e Exposure (too high or too low) or results showing a safety or efficacy concern that could potentially be avoided by altering the RPV dose, as deemed by the sponsor upon IDMC recommendation. Refer to Section 6.6.1 for the dose evaluation criteria. The data may indicate that either all or some participants in certain body weight categories need an adjusted RPV dose.
f An additional intensive PK assessment will be performed after 2 weeks of treatment with the adjusted RPV dose. If after data review by the sponsor and IDMC, the RPV dose is still not acceptable, the process will be repeated until an acceptable RPV dose is found or the criteria for stopping are met.
g Exposure (too high or too low) or results showing a safety or efficacy concern that cannot be avoided by altering the RPV dose, as deemed by the sponsor upon IDMC recommendation. Refer to Section 6.6.1 for the dose evaluation criteria.
h For additional children only, an intensive PK assessment will be performed after 4 weeks of treatment with the RPV dose that was found acceptable in the mini-cohort.
i After at least 12 children with a body weight of <25 kg (in the current study and study C213 combined) received 4 weeks of study treatment (or discontinued earlier), an overall analysis of all available data will be performed for IDMC review purposes. The same dose evaluation process as for the mini-cohort will be followed.
j Approximately 40 participants will be enrolled in study TMC278HTX2002 and C213 Cohort 2 combined; at least 12 participants with a body weight of <25 kg at baseline in total, including at least 7 participants with a body weight of <20 kg at baseline.
k Any retest, of abnormal laboratory results or plasma viral load/resistance testing, should be captured in this TMC278HTX2002 study if the participants roll over to the TMC278IFD3004 study.

1.3 Schedule of Activities

1.3.1 General Schedule of Activities

Study Assessments and Procedures	Screening[a]	Baseline	Study Intervention Phase[b]									Follow-up Visit[b,c]
	W-6	D1	W2	W4[d]	W8	W12	W16	W24	W32	W40	W48[e]	+4 Weeks
Informed consent/assent[f], demographic data, medical and surgical history, concomitant diseases	X											
Inclusion/exclusion criteria[g,mm]	X	X[h]										
Historical HIV-1 genotyping result, including HIV-1 subtype[kk]	X											
HLA-B*5701 testing[i]	X											
Determination of plasma HIV-1 RNA viral load[j]	X	X		X	X	X	X	X	X	X	X	X
Samples for $CD4^+$ cell count	X	X		X	X	X	X	X	X	X	X	
Samples for viral genotyping[k]		X		X	X	X	X	X	X	X	X	X
PBMC sample[l]	X							X			X	
Samples for biochemistry[m,n,o]	X	X	X	X	X	X	X	X	X	X	X	X[p]
Samples for hematology	X	X	X	X	X	X	X	X	X	X	X	X[p]
Samples for endocrine assessments[q,r]		X						X			X[s]	X[p]
Adrenocorticotropic hormone (ACTH) stimulation testing[q,t]	Reflex test											
12-lead ECG[u,mm]	X	X	X	X				X			X[s]	X[p]
Vital signs (pulse rate, blood pressure)	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X[v]	X[w]	X[w]	X	X[w]	X	X[w]	X[w]	X	X[w]
Check occurrence of first menses[x]	X	X	X	X	X	X	X	X	X	X	X	
Tanner staging[y]		X				X		X		X	X	X
Contraceptive counseling[z]	X											
Height/weight[aa]	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[bb]	X	X		X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X		X		X			X[s]	
Samples for PK[j,cc]			X	X[dd]	X	X		X			X	
Diary completion[ee]		X										
Treatment adherence counseling	X	X	X	X	X	X	X	X	X	X	X	
PENTA adherence questionnaire[ll]			X	X	X	X	X	X	X	X	X	
Study intervention accountability			X	X	X	X	X	X	X	X	X	

Study Assessments and Procedures	Screening[a]	Baseline	Study Intervention Phase[b]									Follow-up Visit[b,c]
	W-6	D1	W2	W4[d]	W8	W12	W16	W24	W32	W40	W48[e]	+4 Weeks
Palatability assessment[ff,gg]			X									
Swallowability assessment[ff,hh]			X									
Evaluation of depression[ii]		X		X	X	X	X	X	X	X	X	X
Dispensation of RPV		X		X	X	X	X	X	X	X		
Concomitant therapy[jj]	X	X	X	X	X	X	X	X	X	X	X	X
Observe/Interview for AEs/HIV-related events[jj]	X	X	X	X	X	X	X	X	X	X	X	X

a After obtaining informed consent/assent, samples will be taken for determination of plasma HIV-1 RNA viral load and $CD4^+$ cell count. During the screening phase, it is allowed to assess the plasma viral load and $CD4^+$ cell count separately before the other screening assessments. If plasma viral load results meet the inclusion criteria and the investigator considers continuation of antiretroviral therapy (ART) appropriate (taking into account current treatment guidelines, including $CD4^+$ cell count and the participant's clinical status), the participant will return within 2 weeks after availability of these results for the remainder of the screening procedures. If plasma viral load results do not meet the inclusion criteria, the participant will be considered a screen failure. The baseline visit should be scheduled within 4 weeks after the screening visit (and within 6 weeks after plasma viral load and $CD4^+$ cell count assessments, if these were assessed separately before the other screening assessments). In case of unforeseeable circumstances, the screening phase can be prolonged with maximum 2 weeks resulting in a maximum screening phase duration of 8 weeks.

b Unscheduled visits may be performed for safety/tolerability reasons, including cortisol-related retesting, ECG retesting, and for determination of plasma HIV-1 RNA viral load results.

c The 4-week follow-up visit is performed for participants who do not roll over in the pediatric study TMC278IFD3004, who withdraw from the study on or before the Week 48 visit (unless consent/assent is withdrawn), who have ongoing (S)AEs at the last study visit, or who need retesting of abnormal laboratory results, abnormal ECG, cortisol-related retesting, or plasma viral load/resistance testing at the last study visit. Any retest of abnormal laboratory results or plasma viral load/resistance testing should be captured in this study if the participants roll over to study TMC278IFD3004 or if they stop the study. Additional unscheduled visits may be performed for safety/tolerability reasons, including cortisol-related retesting, ECG retesting, and for confirmation of plasma viral load results.

d For participants with a body weight of <25 kg, the participants and/or their representatives should be contacted via telephone or email to assess adherence (to RPV and other ARVs) and to reinforce study instructions every day for at least 3 consecutive days before the intensive PK sampling. If potential AEs are detected during these telephone/email contacts, then an additional site visit should be scheduled, and necessary evaluations performed. If the participant has missed a dose of RPV within 10 days before the intensive PK visit, the visit should be rescheduled so as to achieve steady state of RPV.

e For participants who discontinue the study before the Week 48 visit, this is the Withdrawal visit.

f Informed consent must be obtained before any study-related activity. Participants (where appropriate, depending on age and local regulation) must be informed about the study and must give assent before any study-related activity.

g Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

h The participant's clinical status will be checked again before the first dose of study treatment. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study treatment is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from study participation.

i Only required for participants for whom the investigator considers abacavir (ABC) in the background regimen and not required for participants with prior documented HLA-B*5701 negative results. Also in case of switch to ABC during the study, the participant should test negative for HLA-B*5701 if prior documented HLA-B*5701 negative results are lacking. The test involves a cheek swab. No eating or drinking is allowed for 30 minutes before the swab.

j In case of suspected virologic failure, a sample for confirmation of plasma viral load and PK should be taken at an unscheduled visit.

k Samples collected at the time of virologic failure, at Weeks 24 and 48, and at the Week 48/Withdrawal visit will be tested for the determination of the HIV-1 genotype, as long as the plasma viral load is sufficiently high. Samples collected at other time points may be selected for the determination of the HIV-1 genotype by the protocol virologist in case of virologic failure and based on plasma viral load.

l A PBMC sample will be taken to allow retrospective characterization of archived viral resistance.

m Sample should be taken after overnight fasting.
n Lipid assessments will only be performed at screening, on Day 1, and at Weeks 24 and 48.
o A hepatitis A, B, and C test will be performed at baseline. Extra tests can be done at other visits, whenever clinically relevant.
p For any abnormal result at the previous visit, the test should be repeated at this visit.
q Only for participants aged ≥6 to <12 years (including for participants who turn 12 years old during the study).
r Assessment of follicle-stimulating hormone (FSH), luteinizing hormone (LH), androstenedione, testosterone, 17-hydroxyprogesterone and dehydroepiandrosterone sulfate (DHEAS) in conjunction with the cortisol assessment.
s Assessments do not need to be performed at the Withdrawal visit.
t The ACTH stimulation test needs to be conducted in case of confirmed abnormally low cortisol (<248 nmol/L [9 µg/dL] or signs or symptoms of adrenal insufficiency. It includes measurements of cortisol and 17-hydroxyprogesterone, measured before and 60 minutes after ACTH stimulation and needs to be conducted in the morning, between 7h30 and 9h30. If the ACTH stimulation test is abnormal (ie, the cortisol value after ACTH stimulation is <500 nmol/L [18.1 µg/dL]), a retest needs to be performed at the next scheduled visit or at least within the next 8 weeks.
u At baseline and at the intensive PK visit, the ECG should be taken predose and at the expected C_{max} (ie, 4 hours after RPV intake). At Weeks 24 and 48, the ECG should preferably be taken at C_{max}. Additional ECGs must be performed in case of start of certain concomitant medication (refer to Section 6.5.2).
v A skin examination only.
w A brief physical examination only.
x Only for girls who have not yet had their first menses. Date of first menses will be noted, as applicable.
y Tanner staging is limited to participants aged ≥6 to <12 years (including participants who turn 12 years old during the study).
z It is the investigator's responsibility to ensure that participants receive counseling about birth control methods and precautions to reduce the risk of transmitting HIV, as appropriate by age (refer to Section 10.4, Appendix 4, Contraceptive and Barrier Guidance and Collection of Pregnancy Information). Girls having their first menses during the study should receive counseling again.
aa Growth will be followed using the standardized growth charts (see Section 10.15).
bb Serum pregnancy test at screening and urine pregnancy test at the other time points (only for girls of childbearing potential). At baseline, the urine pregnancy test will be done before the first RPV intake. Additional serum or urine pregnancy tests may be performed for girls of childbearing potential, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during study participation.
cc Exact date and time of blood sampling and of the last 2 RPV intakes before blood sampling will be recorded on the case report form (CRF). Where possible (ie, if RPV intake occurs during the visit), at least on 1 occasion, the sample will be taken just before RPV intake. When additional safety monitoring ECGs are performed, a PK sample should be taken within 10 minutes after each of these ECGs (refer to Section 6.5.2).
dd For participants with a body weight of <25 kg, intensive PK sampling will take place after 4 weeks of study treatment. Refer to the separate Schedule of Activities for Intensive Pharmacokinetic Sampling for further details. For all other participants, a sparse PK sample will be taken.
ee Participants scheduled for an intensive PK visit and/or their representatives will have to complete a diary documenting RPV intake from the start of study treatment until the intensive PK visit.
ff Questionnaires will only be administered if a certified translation is available in the local language.
gg Assessment should only be done upon administration of the 2.5-mg tablet formulation at the site.
hh Assessment should only be done upon administration of the 25-mg tablet formulation at the site.
ii Evaluation should be done using questionnaires or other means (as available at the site) as part of local standard of care. Any clinically relevant changes occurring during the study will be reported as AEs.
jj Concomitant medication and AEs/HIV-related events (including AIDS-defining illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection) will be monitored throughout the study from signing of the informed consent form (ICF) onwards until the last study-related activity.
kk For children aged ≥2 to <6 years, the availability of a historical HIV-1 genotyping and the HIV-1 subtype result should be documented in the CRF. If a historical HIV-1 genotyping result is available for children aged ≥6 to <12 years, the subtype should be documented in the CRF as well. The historical HIV-1 genotype should be collected by the site monitor and provided to the sponsor.
ll Separate PENTA adherence questionnaires are available for Children ≥ 6 years of age and for caregivers.
mm Retesting for an ECG leading to exclusion will be allowed once.

1.3.2 Schedule of Activities for Intensive Pharmacokinetic Sampling

Note: For participants with a body weight of <25 kg, as defined at baseline, intensive PK sampling will take place after 4 weeks of study treatment. For participants who require an RPV dose adjustment (as per IDMC analysis), intensive PK sampling will take place after 2 weeks of study treatment on that adjusted RPV dose (refer to Section 1.3.3).

Time	Blood Sample[a]	ECG, Pulse Rate, Blood Pressure	Other
			Admission to site in the morning
Predose	X[b]	X[c,d]	Standard breakfast at site
0 h			RPV intake[e]
2 h	X		Resume usual diet
4 h	X	X[d]	
5 h	X		
6 h	X		
9 h	X		
12 h	X		
24 h	X		Discharge from unit[f]

a At each indicated time point, approximately 1 mL of blood will be collected (total volume of blood drawn during the 24-hour period will be approximately 10 mL).
b Within 1 hour before RPV intake.
c Within 2 hours before RPV intake.
d Electrocardiogram and vital sign measurements should be performed preferably before blood sampling.
e Rilpivirine dose should be taken within 40 minutes following the start of the breakfast. For participants who vomit within 30 minutes after dosing, the dose should be readministered. Redosing is not allowed if the participant vomits more than 30 minutes after dosing. If the participant vomits more than 30 minutes after dosing on the day of intensive PK evaluation, this assessment must be rescheduled.
f In case it is not feasible for the participant to stay overnight, the participant can be discharged after the 12-hour sample and return to the site for the 24-hour sample.

1.3.3 Schedule of Activities for Switch to Adjusted RPV Dose (if Applicable)

Note: The following Schedule of Activities is applicable for participants with a body weight of <25 kg who switch to an adjusted RPV dose (as per IDMC analysis).

Study Assessments and Procedures	Study Intervention Phase[a]		
	Dose Switch Visit[b,c]	2 Weeks Post Dose Switch Visit[c,d]	4 Weeks Post Dose Switch Visit[c,e]
Determination of plasma HIV-1 RNA viral load		X	X
Samples for $CD4^+$ cell count		X	X
Samples for viral genotyping[f]			X
Samples for biochemistry[g,h,i]		X	X
Samples for hematology		X	X
12-lead ECG[j]		X	
Vital signs (pulse rate, blood pressure)		X	X
Physical examination		X[k]	X[l]
Check occurrence of first menses[m]		X	X
Height/weight[n]		X	X
Urinalysis		X	
Samples for PK[o]		X[p]	X
Diary completion[q]	X		
Treatment adherence counseling	X	X	X
PENTA adherence questionnaire[r]		X	X
Study intervention accountability		X	X
Palatability assessment[r,s]		X	
Swallowability assessment[r,t]		X	
Evaluation of depression[u]			X
Dispensation of RPV	X		X
Concomitant therapy[v]	X	X	X
Observe/Interview for AEs/HIV-related events[v]	X	X	X

a Unscheduled visits may be performed for safety/tolerability reasons, including cortisol-related retesting and ECG retesting, for PK analysis and confirmation of plasma viral load results (in case of suspected virologic failure), and for the dose switch visit and/or post dose switch visits.

b After at least 4 weeks of study treatment with the RPV dose (15 mg, 12.5 mg, or another adjusted weight-based dose) or, if applicable, with the adjusted RPV dose.

c If the (post) dose switch visit is done within 1 week of the next scheduled visit as indicated in the General Schedule of Activities, this next scheduled visit can be cancelled but assessments of that visit will have to be performed at the (post) dose switch visit.

d A re-evaluation of participants who have been treated with the adjusted RPV dose for 2 weeks (captured as unscheduled visits in the CRF).

e A re-evaluation of participants who have been treated with the adjusted RPV dose for 4 weeks (captured as unscheduled visits in the CRF).

f Samples collected at the time of virologic failure will be tested for the determination of the HIV-1 genotype, as long as the plasma viral load is sufficiently high. Samples collected at other time points may be selected for the determination of the HIV-1 genotype by the protocol virologist in case of virologic failure and based on plasma viral load.

g Sample should be taken after overnight fasting.

h Lipid assessments will not be performed.

i Hepatitis A, B, and C tests can be done, whenever clinically relevant.

j The ECG should preferably be taken at the expected C_{max} (ie, 4 hours after RPV intake). Additional ECGs must be performed in case of start of certain concomitant medication (refer to Section 6.5.2).

k A skin examination only.

l A brief physical examination only.

m Only for girls who have not yet had their first menses. Date of first menses during the study will be noted, as applicable.
n Growth will be followed using the standardized growth charts.
o Exact date and time of blood sampling and of the last 2 RPV intakes before blood sampling will be recorded on the CRF. When additional safety monitoring ECGs are performed, a PK sample should be taken within 10 minutes after each of these ECGs (refer to Section 6.5.2).
p Intensive PK sampling will take place at this visit. Refer to the separate Schedule of Activities for Intensive Pharmacokinetic Sampling for further details.
q Participants and/or their representatives will have to complete a diary documenting RPV intake from the start of treatment (with the adjusted dose) until the intensive PK visit.
r Questionnaire will only be administered if a certified translation is available in the local language.
s Assessment should only be done upon administration of the 2.5-mg tablet formulation.
t Assessment should only be done upon administration of the 25-mg tablet formulation.
u Evaluation should be done using questionnaires or other means (as available at the site) as part of local standard of care. Any clinically relevant changes occurring during the study will be reported as AEs.
v Concomitant medication and AEs/HIV-related events (including AIDS-defining illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection) will be monitored throughout the study from signing of the ICF onwards until the last study-related activity.

2 INTRODUCTION

Rilpivirine (RPV, formerly known as TMC278 [R278474]), a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild type (WT) human immunodeficiency virus type 1 (HIV-1) and against NNRTI-resistant HIV-1 mutants. Rilpivirine as an oral formulation offers the convenience of once-daily dosing with potent antiviral activity and has a favorable safety and tolerability profile in adults and adolescents.

For the most comprehensive nonclinical and clinical information regarding RPV, refer to the latest version of the Investigator's Brochure (IB) and its Addenda for RPV, and to the EDURANT® prescribing information.[13,21]

Throughout this protocol, the term "study intervention" refers to RPV, the term "participant" refers to the child, and the term "representative" refers to the parent(s)/caregiver(s) and/or legally acceptable representative(s).

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1 Study Rationale

Patients infected with HIV-1 are routinely treated with combinations of multiple drugs (highly active antiretroviral [ARV] therapy) including nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs), NNRTIs, protease inhibitors, pharmacokinetic (PK) boosters, integrase inhibitors, and fusion inhibitors. This treatment reduces HIV-1 ribonucleic acid (RNA) to undetectable levels in a substantial proportion of patients and counteracts the risk of viral resistance development. A medical need still exists for the development of age/weight-appropriate formulations in adolescents and children.

Rilpivirine is an NNRTI with in vitro activity against WT and NNRTI-resistant HIV-1. Rilpivirine at a dose of 25 mg once daily has been approved for treatment of ARV treatment-naïve HIV-1-infected adults in multiple countries, including the United States, Canada, Japan, and countries in the European Union, either as a single-agent 25-mg tablet (EDURANT) or as part of several fixed-dose combinations (ie, with the integrase inhibitor dolutegravir [DTG], with tenofovir disoproxil fumarate/emtricitabine [TDF/FTC], and with tenofovir alafenamide/FTC [TAF/FTC]). In most countries, including the United States and countries in the European Union, the indication of EDURANT is restricted to patients with a plasma viral load ≤100,000 HIV-1 RNA copies/mL. In several countries, including the United States and countries in the European Union, this indication has been extended to the pediatric population (ie, adolescents aged ≥12 to <18 years).

The further pediatric development of RPV is ongoing. In Cohort 2 of study TMC278-TiDP38-C213 (C213), an RPV dose that is safe and provides exposures similar to RPV exposures in adults (with a geometric mean area under the plasma concentration-time curve from time of administration up to 24 hours postdose [AUC_{24h}] between 1,426 and 2,673 ng.h/mL) is being evaluated in ARV treatment-naïve HIV-1-infected children aged ≥6 to <12 years with

baseline HIV-1 RNA ≤100,000 copies/mL.[3] Study recruitment has been challenging as the number of children in this specific study population is very limited. The main reasons are that international treatment guidelines generally recommend to initiate antiretroviral therapy (ART) immediately after HIV-1 diagnosis and that many newly identified HIV-1-infected children have HIV-1 RNA levels significantly higher than 100,000 copies/mL. Therefore, the current study is designed to evaluate the PK, safety, tolerability, and efficacy of RPV in combination with other ARVs in virologically suppressed (ie, HIV-1 RNA <50 copies/mL) HIV-1-infected children aged ≥2 to <12 years with a body weight ≥10 kg (ie, the 10th percentile of the growth curve for body weight for healthy girls aged 2 years)[2] and without a history of virologic failure or documented resistance to RPV.

In study C213, available data for children with low body weights (<25 kg) are currently limited. Consequently, in the current study, intensive PK data will be gathered in HIV-1-infected children with a body weight of <25 kg (regardless of age) to further identify an RPV dose that provides exposures similar to those in adults. Depending on the RPV dose, either the oral RPV 25-mg tablet formulation or a not-yet-marketed oral 2.5-mg tablet formulation (to allow dose adaptation) will be administered.

The PK, safety, tolerability, and efficacy data over 48 weeks of treatment with RPV, administered as either a 25-mg dose or a weight-based dose (as applicable), will be evaluated in the entire group of virologically suppressed HIV-1-infected children aged ≥2 to <12 years enrolled in this study. These data will complement the results from Cohort 2 (children aged ≥6 to <12 years) in study C213. With this, the overall regulatory requirements concerning the evaluation of RPV in a pediatric population aged ≥2 to <12 years could be fulfilled (refer to Section 4.2, Scientific Rationale for Study Design).

2.2 Background

Nonclinical Studies

Rilpivirine did not show a potential for genotoxicity, teratogenicity, phototoxicity, skin or eye membrane irritation, or delayed-type hypersensitization. The tumors observed in rodents were not the result of interaction of RPV with deoxyribonucleic acid (DNA) but rather due to an epigenetic mechanism. In addition, RPV did not affect fertility, early embryonic development, pre- and postnatal development, or the immune system at oral doses ranging from 160 to 1,600 mg/kg/day.

The target organs and systems of toxicity observed following oral administration of RPV were the adrenal cortex and the associated steroid biosynthesis (mouse, rat, dog, cynomolgus monkey), the reproductive organs (male and female dog), the liver (mouse, rat, dog), the thyroid and pituitary gland (rat), the kidney (mouse, dog), the hematopoietic system (mouse, rat, dog), and the coagulation system (male rat). The sensitivity of these organs or systems differed by species. In general, the effects were reversible. The effects on the thyroid gland in rats are considered species-specific and not relevant for humans.

Overall, the margin of exposure between that associated with the effects seen in animals after oral dosing and that of the 25-mg once-daily dose of RPV, is considered sufficient in view of the high

sensitivity of animals compared with humans and the lack of relevance of the animal effects for humans.

Rilpivirine is approximately 99.7% bound to plasma proteins in vitro, primarily to albumin. The distribution of RPV into compartments other than plasma (eg, cerebrospinal fluid and genital tract secretions) has not been evaluated in humans. The terminal elimination half-life of RPV is approximately 45 hours. After single dose oral administration of ^{14}C-RPV, on average 85% and 6.1% of the radioactivity could be retrieved in feces and urine, respectively. In feces, unchanged RPV accounted for on average 25% of the administered dose. Only trace amounts of unchanged RPV (<1% of the administered dose) were detected in urine. In vitro experiments indicate that RPV primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP)3A system. All metabolites found in humans were also found in animal species used for safety evaluation. The 25-mg once-daily dose of RPV is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes, or medicinal products transported by P-glycoprotein.[21]

Clinical Studies

At the cut-off date of 19 May 2018, 39 Phase 1 studies with non-HIV-infected adults (878 participants treated with RPV) and 1 Phase 1 study with HIV-1-infected adults (15 participants treated with RPV) had been completed with oral RPV (sponsored by Janssen Research & Development). In 2 Phase 2a studies, 72 HIV-1-infected adults received oral RPV. One Phase 2b and 2 Phase 3 studies, in which 279 and 686 HIV-1-infected adults received oral RPV, respectively, have been completed.[21] Additionally, data up to Week 240 are available from 1 Phase 2 study in 36 HIV-1-infected adolescents (aged ≥12 to <18 years).[4]

Clinical Data and Previous Human Experience With Oral Tablet Formulation of RPV in Adults

Results from pooled Phase 1 studies have provided an understanding of the short-term safety and tolerability profile of RPV and its PK characteristics. Two Phase 2a studies demonstrated the short-term antiviral activity of RPV in HIV-1-infected adults and provided a strong rationale for further development of RPV in HIV-1-infected adults at doses of 25 to 150 mg once daily.

In the Phase 2b study in HIV-1-infected ARV treatment-naïve adults, substantial and sustained virologic response was observed after 96 weeks of study treatment, confirming the results of the primary analysis at Week 48. In the extension after Week 240, all ongoing participants maintained this virologic response up to the end of the study. Rilpivirine provided clear immunologic benefit as shown by the mean increase from baseline in cluster of differentiation (CD)4$^+$ cell counts that occurred in participants treated with RPV up to Week 240. Most adverse events (AEs), including serious adverse events (SAEs) and AEs leading to discontinuation, emerged during the first 48 weeks of study treatment and there were no changes in safety patterns up to the end of the study. The 25-mg once-daily dose of RPV offered the best benefit/risk balance for further development in HIV-1-infected ARV treatment-naïve adults.

The Phase 3 studies TMC278-TiDP6-C209 (C209) and TMC278-TiDP6-C215 (C215) were randomized, double-blind, double-dummy, active-controlled studies in HIV-1-infected ARV treatment-naïve adults. Participants were randomized to receive either RPV 25 mg once daily (686 participants) or efavirenz (EFV) 600 mg once daily (control; 682 participants), in combination with an NRTI background regimen. Rilpivirine 25 mg once daily was generally safe and well tolerated when administered to HIV-1-infected ARV treatment-naïve adults (in combination with 2 NRTIs) for at least 96 weeks, and in the extension beyond 96 weeks, up to study end. In combination with an active background regimen, it has demonstrated substantial and durable efficacy in populations representative of HIV-1-infected ARV treatment-naïve adults. Overall, RPV represents a favorable therapeutic option when considering the efficacy, safety, and tolerability as well as the convenience of once-daily dosing.

The exposure to RPV as the tablet formulation was approximately 40% to 50% lower when taken under fasting conditions or with only a nutritional drink as compared to intake with a standard or high-fat breakfast. Therefore, RPV must always be taken with a meal. The mean steady-state exposure (AUC_{24h}) to RPV after long-term administration (96 weeks) of 25 mg once daily in HIV-1-infected participants was 2.2 µg.h/mL. Steady-state plasma concentrations of RPV were usually reached within 11 days of dosing.

The exposure to RPV can be affected by modulators of CYP3A4 enzyme activity and by drugs that increase the pH. Proton pump inhibitors (eg, omeprazole) should not be coadministered with RPV as this will decrease the exposure to RPV. H_2 receptor antagonists, however, can be used if administered either at least 12 hours before or at least 4 hours after RPV intake, and antacids can be used if administered either at least 2 hours before or at least 4 hours after RPV intake.

Drugs that induce CYP3A4 activity (eg, rifampin and carbamazepine) can reduce RPV exposure and should not be coadministered. Drugs that inhibit CYP3A4 activity (eg, ketoconazole and boosted protease inhibitors) can increase RPV exposure.[21]

CCI [redacted]

Clinical Data and Previous Human Experience With Oral Tablet Formulation of RPV in Adolescents (Aged ≥12 to <18 years) and Children (Aged ≥6 to <12 years)

The Phase 2 study C213 is an ongoing open-label, single-arm study in HIV-1-infected ARV treatment-naïve adolescents (aged ≥12 to <18 years, Cohort 1, completed) and children (aged ≥6 to <12 years, Cohort 2, ongoing). Participants received 48 weeks of treatment with RPV 25 mg once daily in combination with an investigator-selected background regimen (azidothymidine [AZT], abacavir [ABC], or TDF in combination with FTC or lamivudine [3TC]). Participants in Cohort 1 were treated for an additional 4 years. The results of the Week 48 and Week 240 (final) analyses are available for the 36 adolescents enrolled in this cohort.

The Week 48 data showed that the 25-mg once-daily dose of RPV in adolescents resulted in similar RPV exposure as observed in adults.[5] In addition, RPV 25 mg once daily in combination with an investigator-selected background regimen containing 2 N(t)RTIs was efficacious and generally safe and well tolerated.[21]

The results from the Week 240 analysis demonstrated long-term efficacy and safety. Virologic response (defined as confirmed plasma viral load <50 HIV-1 RNA copies/mL, time to loss of virologic response analysis) was achieved in 14/32 participants (43.8%). For participants with baseline plasma viral load ≤100,000 HIV-1 RNA copies/mL, 12/25 participants (48.0%) had virologic response at Week 240, compared with 2/7 participants (28.6%) with baseline plasma viral load >100,000 HIV-1 RNA copies/mL. Most AEs emerged in the first 48 weeks of the study and no new safety signal was observed thereafter. Rilpivirine did not affect pubertal development (as assessed by Tanner staging) or growth of adolescents. There were no new safety findings compared with the known RPV safety profile in HIV-1-infected adults.[4]

The recruitment of children aged ≥6 to <12 years in Cohort 2 is ongoing. The PK data in children (Cohort 2) supplemented with all available data in adolescents (Cohort 1) will allow dose selection for the current study (refer to Section 4.3, Justification for Dose).

2.3 Benefit/Risk Assessment

2.3.1 Known Benefits

The results of this study will establish the RPV dose recommendations for HIV-1-infected children aged ≥2 to <12 years.

2.3.2 Potential Benefits

The establishment of a pediatric RPV dose is an important step towards the development of a pediatric fixed-dose combination with RPV.

Potential benefits of switching to an RPV-based regimen can be expected as treatment with RPV in combination with 2 NRTIs showed an improved safety profile in adults compared with an EFV-based regimen in the Phase 3 studies C209 and C215 (refer to Section 2.2, Background). In addition, oral RPV may show improved palatability versus ritonavir-boosted lopinavir syrup.[7]

Improved palatability in children is important as it plays a pivotal role in achieving patient acceptance and therefore compliance to treatment.

As no control arm is included in the current study, these potential benefits will not be directly assessed.

2.3.3 Known Risks

Every medication can have undesirable effects.

The safety assessment is based on the Week 96 pooled data from 1,368 participants in the Phase 3 controlled studies C209 and C215 in HIV-1-infected ARV treatment-naïve adults, of whom 686 received the 25-mg once-daily dose of RPV (refer to Section 2.2, Background).

Grade 3 or 4 adverse drug reactions (ADRs) were reported in 3.6% of participants treated with RPV. By grouped term, the most frequently reported ADRs were **headache** (15.5%), **nausea** (14.6%), **insomnia** (10.5%), **dizziness** (10.2%), **abnormal dreams** (8.9%), **rash** (7.4%), **abdominal pain** (7.1%), **depression** (6.9%), **fatigue** (5.7%), and **vomiting** (5.4%). Adverse drug reactions of at least grade 2 reported in at least 2.0% of adults treated with RPV were, by grouped term: depression (4.1%), headache (3.5%), insomnia (3.5%), transaminases increased (2.8%), rash (2.3%), and abdominal pain (2.0%).[21] Most ADRs occurred in the first 48 weeks of study treatment.[13]

There were no additional ADR terms identified in adults in the (pooled) Phase 1, Phase 2a, and Phase 2b (up to 240 weeks) studies, nor in the post-Week 96 analyses of the Phase 3 studies.[21]

Furthermore, no new safety signal was identified in adolescents (Cohort 1 in the pediatric study C213) after 240 weeks of study treatment when compared with the known RPV safety profile in HIV-1-infected adults.[4]

2.3.4 Potential Risks

As with all clinical studies requiring blood sampling, there are risks associated with **venipuncture** and **multiple blood sample collection**. Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and, rarely, infection at the site where the blood is drawn.

Virologic failure and development of resistance are known to occur in ART containing an NNRTI and can result in the loss of treatment options from this class and of other constituents of the ART. In participants treated with RPV, a higher rate of overall treatment resistance and cross-resistance to the NNRTI class was observed compared to control. In the Phase 3 studies, the risk of virologic failure was greater in participants with a baseline plasma viral load >100,000 HIV-1 RNA copies/mL than in participants with a baseline plasma viral load ≤100,000 HIV-1 RNA copies/mL. The greater risk of virologic failure for participants treated with RPV was observed in the first 48 weeks of study treatment, while low rates of virologic failure (similar to the control) were observed from Week 48 to Week 96. Participants who experienced virologic failure had an increased risk of developing NNRTI and/or N(t)RTI resistance. In the

Phase 2 study in adolescents, no new information on the resistance profile of RPV was identified in the Week 48 resistance analysis.[11,21]

The concomitant use of RPV and other drugs may result in potentially significant **drug interactions**, some of which may lead to loss of therapeutic effect of RPV and possible development of resistance.[13]

Body fat redistribution/accumulation, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and 'cushingoid appearance' have been observed in patients receiving ART. The mechanism and long-term consequences of these events are unknown. A causal relationship has not been established.[21]

Immune reconstitution inflammatory syndrome has been reported in participants treated with combination ART, including RPV. During the initial phase of combination ART, participants whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders such as Graves' disease have also been reported to occur in the setting of immune reconstitution inflammatory syndrome; however, the time to onset is more variable, and these events can occur many months after treatment initiation.[21]

2.3.5 Overall Benefit/Risk Assessment

Accumulated data from completed and ongoing studies indicate that the benefit/risk balance for RPV clinical studies is positive.

Although there are potential benefits (refer to Section 2.3.2), there is no known direct benefit expected for HIV-1-infected participants in the current study (refer to Section 2.3.1).

Several safety measures have been proposed to minimize risk to participants, including:

- Utilization of selection criteria which exclude participants who may potentially be at higher risk of an AE (refer to Section 5, Study Population).
- Utilization of withdrawal criteria (refer to Section 7.2, Participant Discontinuation/Withdrawal From the Study). If a participant discontinues study intervention and withdraws from the study before the end of the study intervention phase (except when due to withdrawal of consent/assent), the Week 48/Withdrawal visit and 4-week follow-up visit assessments should be obtained.
- Participants experiencing rash, acute systemic allergic reactions, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevations, pancreatic amylase or lipase elevations, clinical hepatitis, nausea, diarrhea, neuropsychological symptoms, signs and symptoms of adrenal insufficiency, or other toxicities will be closely monitored, as specified in the protocol (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities).

- For participants who do not roll over in the pediatric study TMC278IFD3004, any clinically significant abnormalities persisting at the last study visit will be followed up by the investigator until resolution or until a clinically stable endpoint is reached (refer to Section 8.2, Safety Assessments).
- An Independent Data Monitoring Committee (IDMC) will evaluate the safety data on an ongoing basis.
- In participants with a body weight of <25 kg, the appropriate RPV dose will be investigated in more detail and reviewed by the sponsor and the IDMC.
- Safety evaluations will be done at several time points throughout the study (refer to Schedule of Activities). Blood samples for biochemistry, hematology, and endocrine assessments (only for participants aged ≥6 to <12 years, including participants who turn 12 years on the study), and urine samples for urinalysis will be collected, and adrenocorticotropic hormone (ACTH) stimulation testing (only for participants aged ≥6 to <12 years, including participants who turn 12 years on the study) will be performed if required (refer to Section 1.3.1, General Schedule of Activities). Vital signs and 12-lead electrocardiograms (ECGs) will be recorded and physical examinations, including Tanner staging in participants aged ≥6 to <12 years (including participants who turn 12 years on the study) and height and weight measurements, will be performed. In addition, depression will be evaluated. Treatment can be stopped or interrupted at the investigator's discretion (refer to Section 7, Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal).
- To avoid the accumulation of resistance-associated mutations (RAMs) and to allow timely study withdrawal, frequent plasma HIV-1 RNA viral load monitoring will be performed in addition to real-time plasma-based viral resistance testing in case of loss of virologic response. To minimize the risk of re-emergence of archived viral resistance, participants will only be enrolled if no documented genotypic evidence of resistance to RPV or to the selected background ARVs is present (refer to Section 5.2, Exclusion Criteria).
- Additional ECGs will be performed in case of start of certain concomitant medication (refer to Section 6.5.2).
- The blood sample collection scheme is designed to perform safety, tolerability, and efficacy evaluations and to accurately and completely describe the PK of RPV with a minimum number of blood samples being collected. The total blood volume to be collected is considered to be an acceptable amount over this time period from the population in this study (refer to Section 4.2.1, Study-specific Ethical Design Considerations). The use of indwelling catheters is encouraged for the intensive PK sampling to minimize discomfort and distress due to repeated venipunctures for blood sampling. Furthermore, local anesthetics can be used at the blood sampling site.
- Pregnancy and breastfeeding (if applicable/appropriate by age) are exclusion criteria. In addition, all participants are required to use contraceptive methods, as detailed in Section 5.

More detailed information about the known and expected benefits and risks of RPV may be found in the IB for RPV and its Addenda, and in the EDURANT prescribing information.[13,21]

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objectives

- To evaluate the steady-state PK of RPV and determine the appropriate dose of RPV in combination with other ARVs in participants aged ≥2 to <12 years with a body weight of <25 kg.
- To evaluate the safety and tolerability of RPV in combination with other ARVs in participants aged ≥2 to <12 years over a 24-week treatment period.

Secondary Objectives

- To evaluate the safety and tolerability of RPV in combination with other ARVs over a 48-week treatment period.
- To evaluate the efficacy of RPV in combination with other ARVs over a 24- and 48-week treatment period.
- To evaluate population PK and PK/pharmacodynamic (PD) relationships for safety and efficacy of RPV in combination with other ARVs.
- To assess resistance in case of loss of virologic response to RPV in combination with other ARVs.
- To evaluate treatment adherence to RPV in combination with other ARVs over a 24- and 48-week treatment period.

Exploratory Objectives

- To assess the palatability of the 2.5-mg tablet formulation of RPV, if applicable.
- To assess the swallowability of the 25-mg tablet formulation of RPV, if applicable.
- To assess archived viral resistance, if feasible depending on available blood volume.

ENDPOINTS

Primary Endpoints

- Area under the plasma concentration-time curve from time of administration up to 24 hours postdose of RPV, as derived from the intensive PK assessments.
- Incidence of grade 3/4 AEs, SAEs, HIV-related events (including acquired immune deficiency syndrome [AIDS]-defining illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection), and AEs leading to discontinuation of study intervention through 24 weeks of study treatment.

Secondary Endpoints

- Incidence and severity of AEs/HIV-related events and their relatedness to RPV through 24 and 48 weeks of study treatment.

- Change from baseline over time and shift in toxicity grades/abnormalities versus reference for clinical laboratory parameters, ECG parameters, vital signs, and physical examination through 24 and 48 weeks of study treatment.
- Proportion of participants with HIV-1 RNA <50 and ≥50 copies/mL using the Food and Drug Administration (FDA) Snapshot approach through 24 and 48 weeks of study treatment.
- Proportion of participants with HIV-1 RNA <400 and ≥400 copies/mL using the FDA Snapshot approach through 24 and 48 weeks of study treatment.
- Immunologic changes, measured by $CD4^+$ cell count (absolute and percentage relative to total lymphocytes), through 24 and 48 weeks of study treatment.
- Pharmacokinetic parameters of RPV (other than area under the plasma concentration-time curve [AUC]), as derived from the intensive PK assessments.
- Pharmacokinetic parameters of RPV, as derived by population PK modeling, through 24 and 48 weeks of study treatment.
- Viral genotype at the time of virologic failure through 24 and 48 weeks of study treatment.
- Treatment adherence, as assessed by the Pediatric European Network for the Treatment of AIDS (PENTA) adherence questionnaire and by study intervention accountability, through 24 and 48 weeks of study treatment.

Exploratory Endpoints

- Responses to the palatability questionnaire after 2 weeks of study treatment.
- Responses to the swallowability questionnaire after 2 weeks of study treatment.
- Mutations in HIV-1 DNA or in HIV-1 RNA, as assessed by retrospective peripheral blood mononuclear cell (PBMC)- or plasma-based analyses, through 24 and 48 weeks of study treatment.

Refer to Section 8, Study Assessments and Procedures, for evaluations related to endpoints.

HYPOTHESIS

No formal hypothesis will be tested.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, open-label, single-arm, multicenter, interventional study in HIV-1-infected participants (boys and girls) aged ≥2 to <12 years with a body weight of at least 10 kg to evaluate the PK, safety, tolerability, and efficacy of switching to RPV once daily in combination with other, investigator-selected ARVs (refer to Section 6.5.1).

To comply with overall regulatory requirements, approximately 40 participants (including at least 12 participants with a body weight of <25 kg at baseline) will be enrolled in this study and in Cohort 2 (participants aged ≥6 to <12 years) of study C213 combined. A target of approximately 25 to 30 participants will be enrolled in this study. The actual number of participants in this study

will depend on the number of participants enrolled in Cohort 2 of study C213. The participants with a body weight of <25 kg and ≥25 kg will be enrolled in parallel.

Each participant needs to be virologically suppressed (ie, HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months at screening and needs to have no history of virologic failure. In addition, the participants should lack any RPV RAMs as evidenced by their historical HIV-1 genotyping results, if available. Participants aged ≥2 to <6 years, however, are required to have historical HIV-1 genotyping results available at screening, to be provided to the sponsor. The availability of the historical HIV-1 genotyping results and the subtype need to be recorded in the CRF. For participants aged ≥6 to <12 years, the availability of historical HIV-1 genotyping results should be recorded in the CRF. More details on the study population are provided in Section 5.

Rilpivirine (25 mg, 15 mg, 12.5 mg, or another adjusted weight-based dose) will be orally administered once daily in combination with an investigator-selected background regimen containing other ARVs such as N(t)RTIs and integrase inhibitors. Protease inhibitors and ARVs requiring a PK booster, however, are disallowed from baseline onwards (refer to Section 6.5 for an overview of allowed and disallowed concomitant therapy). In participants with a body weight of <25 kg, an intensive PK assessment will be performed after 4 weeks of study treatment to evaluate the appropriateness of their RPV dose. If the RPV dose needs to be adjusted, an additional intensive PK assessment will be performed after 2 weeks of treatment with the adjusted RPV dose to evaluate the dose modification. Refer to Figure 1 for a schematic overview of the study and the dose evaluation process. For the dose evaluation criteria, refer to Section 6.6.1.

At some sites, an optional PK substudy may be performed to collect intensive PK data in children ≥6 years with body weight ≥25 kg on the day of intensive PK (substudy), which would require additional assessments as specified in the substudy protocol.

The decision to modify the RPV dose for a specific group of participants will be made by the sponsor upon IDMC recommendation. CCI [redacted]

Refer to Section 6 for further information on the study intervention. Criteria for discontinuation of the study intervention and participant discontinuation/withdrawal from the study are listed in Section 7.

The participants will continue the study intervention and ARV background regimen (through the data review periods, if applicable) until they all reach a total treatment duration of 48 weeks (or discontinue earlier). Dose adjustments of RPV due to changes in body weight, if applicable, are allowed.

All participants will have a screening phase aimed to be completed within 6 weeks. However, the screening phase can be prolonged with maximum 2 weeks in case of unforeseeable circumstances. All participants will receive open-label treatment for 48 weeks in the study intervention phase. Upon study completion, participants who continue to experience clinical benefit from treatment

with RPV will be offered the opportunity to continue study treatment in the pediatric rollover study TMC278IFD3004. The total study duration for each participant, including screening and study intervention phases, will be approximately 54 weeks. Participants who do not roll over in the pediatric study TMC278IFD3004, who withdraw from the study on or before the Week 48 visit (unless consent/assent is withdrawn), who have ongoing (S)AEs at the last study visit, or who need retesting of abnormal laboratory results, abnormal ECG, cortisol-related retesting, or plasma viral load/resistance testing at the last study visit will have a follow-up visit 4 weeks after their last study visit. Any retest of abnormal laboratory results or plasma viral load/resistance testing should be captured in this study if the participants roll over to study TMC278IFD3004.

Pharmacokinetic parameters will be derived from the intensive PK assessments performed in participants with a body weight of <25 kg. CCI [redacted]

Key safety assessments will include the monitoring of (S)AEs and HIV-related events (including AIDS-defining illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection [cut-off for Stage-3 illnesses is 6 years of age per criteria from 2014]),[1] clinical laboratory tests (including endocrine assessments in participants aged ≥6 to <12 years, including participants who turn 12 years old during the study), cardiovascular safety monitoring (vital signs and 12-lead ECGs), and physical examination (including growth). In addition, an evaluation of depression will be performed using questionnaires or other means (as available at the site) as part of local standard of care for this population (refer to Section 8.2).

Key efficacy assessments include determination of plasma HIV-1 RNA viral load and measurement of $CD4^+$ cell count (refer to Section 8.1).

Other assessments and procedures include resistance testing through HIV-1 genotyping and a retrospective evaluation of RAMs in PBMCs, documenting RPV intake through diary completion (only for participants scheduled for an intensive PK visit), treatment adherence, and palatability and swallowability assessments (refer to Section 8.10).

Details on the timing of the study intervention administration and assessments are given in the Schedule of Activities.

The same IDMC as for the study C213 will be commissioned for this study. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations, for details. IDMC analyses will be conducted as described in Section 9.5. The primary analysis (with formal database lock) will be done when all participants have reached Week 24 (or discontinued earlier) followed by a final analysis (with formal database lock) when all participants have reached Week 48 (or discontinued earlier).

4.2 Scientific Rationale for Study Design

Study Design

An open-label study design in which participants receive multiple doses of a certain study intervention up to steady state is a widely accepted design for studies in which a primary objective is to assess the steady-state PK parameters (ie, an objective measure) and to determine the appropriate dose of that study intervention. The PK data in children with a body weight of <25 kg gathered in this study (combined with the PK data in children with a body weight of <25kg in study C213) will allow for comparison with historical data obtained in adults to determine if similar exposures as those in adults are achieved. For this study, AUC_{24h} of a selected RPV dose under fed and steady-state conditions will be the primary PK parameter. The target geometric mean AUC_{24h} for RPV in this study population is between 80% and 150% of the observed geometric mean AUC_{24h} for RPV in HIV-1-infected adults from the Phase 3 PK substudies of C209 and C215 (ie, between 1,426 and 2,673 ng.h/mL).[3] Pharmacokinetic data from adolescents will also be considered in the evaluation.[5] While the AUC_{24h} for RPV will be the primary PK parameter, the maximum observed plasma concentration (C_{max}) and the (trough) plasma concentration at the beginning (C_{0h}) and/or end (ie, at 24 hours postdose [C_{24h}]) of the RPV dosing interval will also be considered.

In this study, participants will switch to RPV plus other ARVs. This approach is supported by several studies indicating that switching to an RPV-containing ARV regimen is non-inferior in terms of safety, tolerability, efficacy, and the occurrence of virologic failure.[6,9,17]

Several safety measures have been proposed to minimize risk to participants (as described in Section 2.3.5, Overall Benefit/Risk Assessment) because only limited data are available on safety and tolerability in children aged ≥2 to <12 years. The primary objective will be the evaluation of safety and tolerability of RPV in combination with other ARVs in all participants. In addition, for participants with a body weight of <25 kg, the appropriateness of the RPV dose will first be assessed in a mini-cohort of at least 5 participants. Only when the results are deemed satisfactory by the sponsor upon IDMC recommendation (ie, satisfactory exposure and results not showing any safety or efficacy concern), additional participants with a body weight of <25 kg will be recruited (refer to Figure 1).

Study Population

Due to the medical need for the development of novel potent ARVs and age/weight-appropriate formulations in children (refer to Section 2.1, Study Rationale), HIV-1-infected children (boys and girls) aged ≥2 to <12 years will be enrolled. The recruitment of ARV treatment-naïve children in Cohort 2 in the ongoing study C213 is challenging (refer to Section 2.1).[4] Therefore, recruitment in the current study is facilitated by enrolling participants who are virologically suppressed on a stable ARV regimen. The actual number of participants in this study will depend on the number of participants enrolled in Cohort 2 in study C213 (refer to Section 4.1).

Children with HIV-infection are known to often present with a stunted growth and a low body weight compared with healthy children, even more so if additional risk factors for growth impairment are present.[33] To ensure that a representative fraction of the HIV-1-infected pediatric population can be studied, children with a body weight as of 10 kg (ie, the 10th percentile of the growth curve for body weight for healthy girls aged 2 years)[2] are allowed to enter the study.

In clinical studies, hypersensitivity reactions have been reported in approximately 5% of adult and pediatric participants receiving ABC.[30] Since the risk for developing such reactions has been linked to the presence of the human leukocyte antigen (HLA)-B*5701 allele,[28] participants without prior documented HLA-B*5701 negative results for whom the investigator considers ABC in the background regimen should test negative for HLA-B*5701 at screening to limit the risk of hypersensitivity reactions (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities, for details). If a switch to an ABC-containing background regimen is planned during the study (due to intolerance, refer to Section 10.2), an HLA-B*5701 test has to be performed to determine eligibility to start ABC treatment (unless prior documented negative results are available).

Study Intervention Administration

The combined use of multiple ARVs in HIV-1-infected participants is currently recommended due to the inherent high mutation rate of HIV.[8,10] Therefore, all participants will receive an investigator-selected background regimen in addition to RPV (refer to Section 6.5). Consistent with the treatment guidelines for ART, sensitivity to the chosen ARVs will be established at screening using historical HIV-1 genotyping results. Participants aged ≥6 to <12 years are not required to have historical HIV-1 genotyping results available at screening due to limited availability of historical HIV-1 genotyping results for participants in this age group, especially in the developing countries, and the expected fading of HIV-1 mutations.[16,22,23,25]

The 25-mg once-daily dose of RPV has been approved for oral treatment of ARV treatment-naïve HIV-1-infected adults and adolescents in multiple countries. The appropriate RPV doses to be used across the whole body weight range will be further established in this study. CCI [redacted].

Pharmacokinetic evaluations have shown that RPV is better absorbed following oral administration with food (refer to Section 2.2, Background). Therefore, RPV intake should occur with a meal.

Data collected over 24 weeks (primary analysis) are deemed a reasonable basis to adequately establish safety, tolerability, and efficacy.[15] Longer-term safety, tolerability, and efficacy data will be reported after an additional 24-week treatment period at Week 48 (final analysis).

Study Assessments

To ensure that RPV steady-state is achieved after switching from the original ARV regimen, the 24-hour intensive PK assessment will be performed after 4 weeks of study treatment. The blood sample collection scheme was designed to accurately and completely describe the PK of RPV with a minimum number of blood samples being collected.

To avoid the accumulation of RAMs and to allow timely study withdrawal, frequent plasma viral load monitoring will be performed in addition to real-time plasma-based viral resistance testing in case of loss of virologic response. Samples for determination of $CD4^+$ cell count will be taken in addition to the plasma viral load samples.

Nonclinical studies demonstrated changes in adrenal hormones (refer to Section 2.2, Background). As a precaution, clinical laboratory evaluations will also include endocrine assessments in participants aged ≥6 to <12 years (including participants who turn 12 years old during the study) to verify whether any clinically relevant adrenal or gonadal effects of RPV are observed (refer to Section 8.2.4).

Delusions and inappropriate behavior have been reported in participants receiving licensed NNRTIs, predominantly in participants with a history of mental illness or substance abuse. In study C213, 19.4% of ARV treatment-naïve HIV-1-infected adolescents aged ≥12 to <18 years receiving the 25-mg once-daily dose of RPV were reported with depression at the Week 48 analysis cut-off. To proactively assess the risk of depression in participants treated with RPV, an evaluation will be done using questionnaires or other means (as available at the site) as part of local standard of care for this population. This will determine who needs to be referred for a complete mental health assessment by a mental health professional. Any clinically relevant changes occurring during the study will be reported as AEs.

Drug adherence is critical to the success of any treatment regimen. In addition, in the current study, suboptimal adherence to RPV has an impact on the PK assessments of RPV. Moreover, poor adherence to the background ARV regimen while remaining on only RPV (ie, virtual monotherapy) could not only lead to incomplete suppression of viral replication and treatment failure, but also potentially result in the emergence of a drug-resistant virus. There is evidence that adherence problems occur frequently in children. In a randomized treatment study, caregivers reported that 30% of children missed 1 or more doses of ARVs in the preceding 3 days.[36] These findings illustrate the difficulty of maintaining high adherence levels, and underscore the need to work in partnership with families to make adherence assessment, education, and support integral components of care. In the current study, compliance to RPV and the background ARVs will be assessed by the PENTA adherence questionnaire. Compliance to RPV will also be assessed via pill count (study intervention accountability). If a participant's intake of RPV or background ARVs is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

Understanding the palatability and/or swallowability of the study intervention for children is important as it plays a pivotal role in achieving patient acceptance and therefore compliance to treatment. Palatability and swallowability will be assessed using a questionnaire by documenting the participant's reaction when he or she is given the study intervention (refer to Sections 10.11 and 10.12, respectively).

4.2.1 Study-specific Ethical Design Considerations

Potential participants and/or their representatives will be fully informed of the risks and requirements of the study and, during the study, participants and/or their representatives will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants and/or their representatives who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent/assent voluntarily will be enrolled.

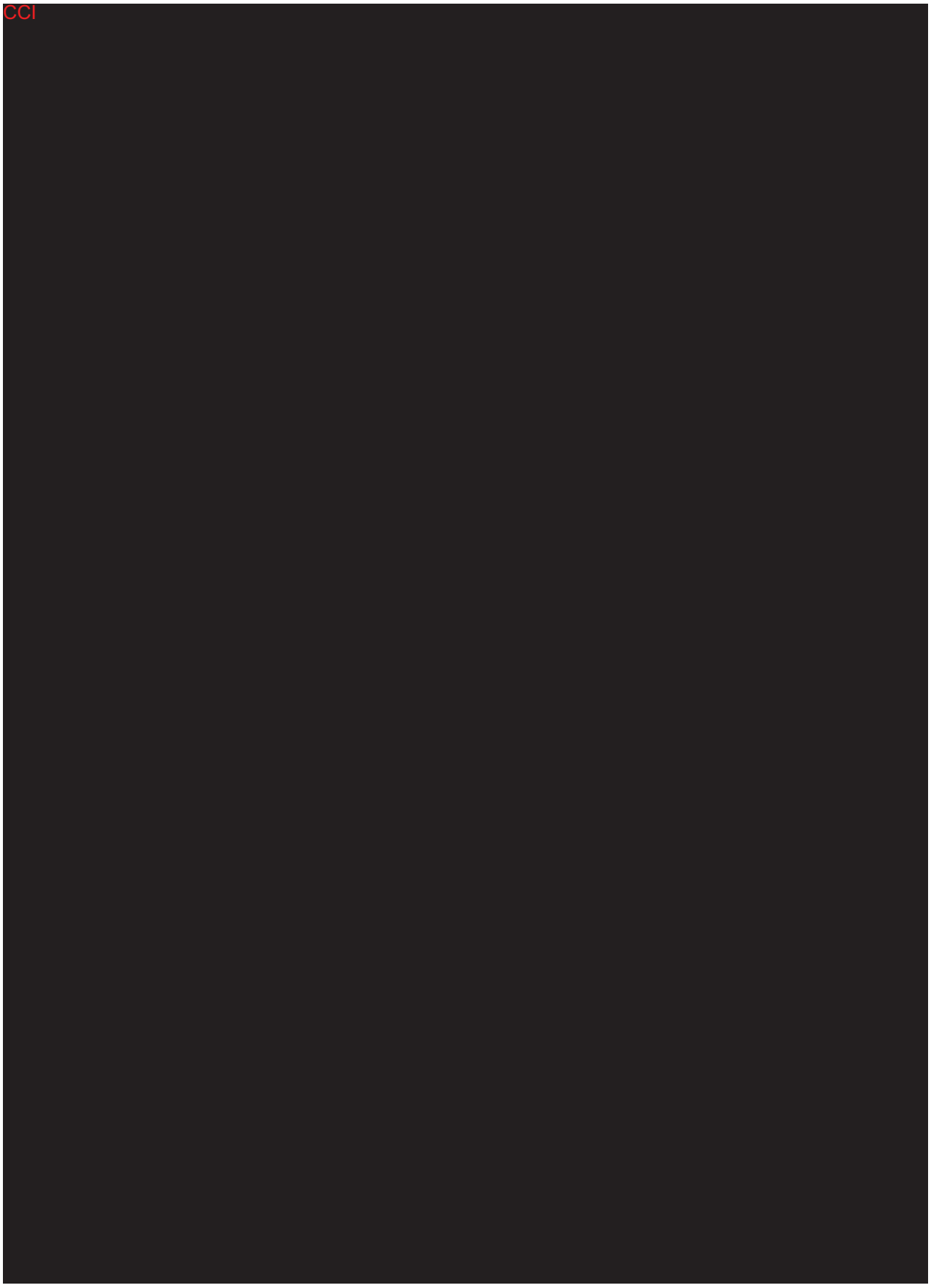
When referring to the signing of the informed consent form (ICF), the term representative refers to the parent(s)/caregiver(s) and/or legally acceptable representative(s) of the child with authority to authorize participation in research. For each participant, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants aged ≥7 years, depending on the institutional policies. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their representatives still want them to participate (refer to Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations).

This study is being conducted to obtain data needed to assist in further pediatric development of RPV and establishing dose adjustment guidance in children. The primary ethical concern is that this study will be performed in HIV-1-infected participants who will switch from an effective, suppressive ARV regimen to an RPV-based regimen still under investigation in this population. Known and potential benefits/risks are described in Section 2.3. Participants will receive financial compensation for travel expenses.

The total blood volume to be collected over a 30-day period is considered to be an acceptable amount over this time period from this study population based upon pediatric standards.[14,19,37]

4.3 Justification for Dose

CCI [redacted]


CCI

CCI [redacted]

4.4 End of Study Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 48 of the study intervention phase. Participants who prematurely discontinue study intervention for any reason before completion of the study intervention phase will not be considered to have completed the study.

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

5 STUDY POPULATION

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures, for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1 Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Aged ≥2 to <12 years at screening.

2. Criterion modified per Amendment 3

   2.1 Weighing at least 10 kg at screening.

3. Have documented chronic HIV-1 infection.

4. Criterion modified per Amendment 1 and Amendment 2

   4.1 On a stable ARV regimen for at least 6 months prior to screening and virologically suppressed with documented evidence of at least 2 plasma viral loads <50 HIV-1 RNA copies/mL: one within 2-12 months prior to screening and one at screening.

   Note: single viral loads ≥50 HIV-1 RNA copies/mL ('blips') are allowed after viral suppression (confirmed viral load <50 HIV-1 RNA copies/mL) within 12 months prior to screening, provided a subsequent viral load measurement is <50 HIV-1 RNA copies/mL (or HIV-1 RNA undetectable by a local HIV-1 RNA test) prior to or at screening.

5. Criterion deleted per Amendment 1.

6. Parent(s) (preferably both if available or as per local requirements) (or the participant's legally acceptable representative[s]) must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to allow the child to participate in the study. Assent is also required from participants capable of understanding the nature of the study (typically aged ≥7 years), as described in the Informed Consent Process in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

7. Can comply with the protocol requirements.

8. Can switch from any ARV class.

9. Never been treated with a therapeutic HIV vaccine.

10. Otherwise healthy and medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.

11. Otherwise healthy on the basis of clinical laboratory tests performed at screening. If the results of biochemistry, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.

12. Historical HIV-1 genotyping result at screening for children aged ≥2 to <6 years (and for children aged ≥6 to <12 years if a historical HIV-1 genotyping result is available at screening) must demonstrate sensitivity to RPV and to the selected background ARVs.

13. Girls are eligible to participate if they are not pregnant (refer to Section 10.4, Appendix 4, Contraceptive and Barrier Guidance and Collection of Pregnancy Information) and not breastfeeding.

14. Girls of childbearing potential must have a negative highly sensitive serum β-human chorionic gonadotropin test at screening.

15. Heterosexually active girls of childbearing potential must practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method while receiving study treatment and for at least 30 days after last RPV intake (refer to Section 10.4, Appendix 4, Contraceptive and Barrier Guidance and Collection of Pregnancy Information).

16. Heterosexually active boys must practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method while receiving study treatment and for at least 30 days after last RPV intake. All HIV-1-infected boys are advised to use a condom to reduce the risk of transmitting HIV (refer to Section 10.4, Appendix 4, Contraceptive and Barrier Guidance and Collection of Pregnancy Information).

17. Can adhere to the lifestyle restrictions (refer to Section 5.2).

5.2 Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Have previously documented HIV-2 infection.

2. Have known or suspected acute (primary) HIV-1 infection.

3. Taken any disallowed concomitant therapies within 4 weeks before the planned first dose of study intervention (refer to Section 6.5, Concomitant Therapy).

4. A positive HLA-B*5701 test at screening (when the investigator considers ABC in the background regimen). In case of a positive test, ABC cannot be administered, but instead, the investigator can select another ARV in the background regimen. HLA-B*5701 testing is not required for participants with prior documented negative results.

5. Any current or history of adrenal disorder.

6. Any active clinically significant diseases (eg, pancreatitis, cardiac dysfunction, active and significant psychiatric disorders, clinical suspicion of adrenal insufficiency, and

hepatic impairment) or findings at screening or medical history that, in the investigator's opinion, would compromise the outcome of the study.

7. A history of virologic failure to ARVs with or without availability of an HIV-1 genotype result at the time of failure.

8. Documented genotypic evidence of resistance to RPV or to the selected background ARVs from historical data available in the source documents (ie, at least 1 NNRTI RAM from the following list compiled on the basis of the list of the International Antiviral Society United States of America [IAS-USA] NNRTI RAMs[39] and other relevant publications).

A098G	V106M	Y181C	G190S
L100I	V108I	Y181I	G190T
K101E	E138A	Y181V	P225H
K101P	E138G	Y188C	F227C
K101Q	E138K	Y188H	M230I
K103H	E138Q	Y188L	M230L
K103N	E138R	G190A	P236L
K103S	V179E	G190C	K238N
K103T	V179D	G190E	K238T
V106A	V179T	G190Q	Y318F

9. A known clinically significant allergy, hypersensitivity, or intolerance to RPV or its excipients (refer to the latest version of the IB for RPV)[21] or to the selected background ARVs.

10. Criterion modified per Amendment 1

10.1 Received an investigational intervention (including investigational vaccines) containing an active substance or used an invasive investigational medical device within 90 days before the planned first dose of study intervention.

11. Enrolled in clinical studies that include any blood sampling with a volume >50 mL taken within 6 months before the planned first administration of RPV, specimen collection, or other interventional procedure. Concurrent participation in non-interventional observational studies is allowed as long as there is no impact on the objectives of this study. Data collected in this study can be reported in the observational study.

12. Any condition (including but not limited to the abuse of alcohol or drugs [eg, barbiturates, opiates, cocaine, cannabinoids, amphetamines, and benzodiazepines]) for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

13. A life expectancy of less than 6 months.

14. Any currently active AIDS-defining illness or Stage-3-defining Opportunistic Illnesses in HIV Infection (cut-off for Stage-3 illnesses is 6 years of age per criteria from 2014).[1]

Note: An AIDS-defining illness not clinically stabilized for at least 30 days will be considered as clinically active.

Note: Primary and secondary prophylaxis for an AIDS-defining illness is allowed in case the medication used is not part of the disallowed medication (refer to Section 6.5.3).

15. Any grade 3/4 laboratory abnormality at screening according to the Division of AIDS (DAIDS) grading table (refer to Section 10.5, Appendix 5, DAIDS Table), except for a selection of abnormalities:

a) grade 3 absolute neutrophil count

b) grade 3 platelets

c) grade 3 glucose elevation in diabetics

d) asymptomatic grade 3 pancreatic amylase elevation

e) asymptomatic grade 3 triglyceride / cholesterol / glucose elevation

f) asymptomatic grade 4 triglyceride elevation

Note: Retesting of abnormal screening values that lead to exclusion will be allowed only once for each laboratory test using an unscheduled visit during the screening phase (to reassess eligibility).

16. Active tuberculosis or being treated for tuberculosis with rifamycins at screening.

17. The following ECG findings at screening, if judged clinically significant by the investigator: abnormal pulse rate and QRS intervals; rhythm abnormalities; evidence of acute ischemic changes.

18. Criterion modified per Amendment 3

18.1 One or more of the following risk factors for QTc prolongation:

a) a confirmed prolongation of QT/QTc interval, eg, repeated demonstration of QT interval corrected for heart rate according to Bazett's formula (QTcB) or Fridericia's formula (QTcF) ≥450 ms in the screening ECG.

b) pathological Q-waves (defined as Q-wave >40 ms or depth >0.4-0.5 mV).

c) evidence of ventricular pre-excitation.

d) electrocardiographic evidence of complete or incomplete left bundle branch block or complete or clinically significant incomplete right bundle branch block.

e) evidence of second or third degree heart block.

f) intraventricular conduction delay with QRS duration >90 ms, unless this is the only conduction abnormality, and no other conduction abnormalities are present.

g) bradycardia as defined by sinus rate <50 bpm.

h) personal or family history of long QT syndrome.

i) personal history of cardiac disease (including congenital heart disease), or symptomatic arrhythmias, with the exception of sinus arrhythmia; personal history of asymptomatic arrhythmias is excluded if the asymptomatic arrhythmia is clinically significant in the opinion of the investigator.

j) syncopal episodes if repeated, unexplained, and unrelated to emotional distress

k) risk factors for Torsade de Pointes (TdP) (eg, heart failure, hypokalemia, and hypomagnesemia).

Note: Retesting of an abnormal screening ECG that leads to exclusion will be allowed only once using an unscheduled visit during the screening period (to reassess eligibility).

19. Acute clinical hepatitis at screening.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting and rescreening. The required source documents to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

5.3 Lifestyle Considerations

Potential participants must adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements) (refer to Sections 5.1 and 5.2, respectively).

Participants scheduled for an intensive PK visit must adhere to the following meals and dietary restrictions (as appropriate for the participant’s age) until the last PK sample at the intensive PK visit has been taken:

1. Consumption of Seville oranges, grapefruit or grapefruit juice, apple juice, orange juice, and citrus fruits is not permitted from 7 days before RPV intake on the day of the intensive PK sampling until the last PK sample at the intensive PK visit has been taken.

2. Quinine-containing products (eg, tonic water and bitter lemon) are not permitted from 24 hours before RPV intake on the day of the intensive PK sampling until the last PK sample at the intensive PK visit has been taken.

3. Alcohol-containing products are not permitted from 24 hours before RPV intake on the day of the intensive PK sampling until the last PK sample at the intensive PK visit has been taken.

5.4 Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Retesting

Any grade 3/4 laboratory abnormalities or ECG abnormalities at screening that lead to exclusion are allowed to be retested once as described in exclusion criteria 15 and 18 in Section 5.2. Retesting will take place during an unscheduled visit in the screening phase.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. In case the inclusion or exclusion criteria are updated, a participant may be rescreened one additional time. Participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase.

6 STUDY INTERVENTION

6.1 Study Interventions Administered

Two formulations of RPV may be used in this study:

! The commercially available RPV (EDURANT) is formulated as an oral film-coated tablet (formulation GFI-314585-CA-026), containing 27.5 mg of RPV as the hydrochloric acid salt R314585, equivalent to 25 mg of RPV as the free base.

CCI

The study intervention (RPV 25 mg, 15 mg, 12.5 mg or another adjusted weight-based dose) will be provided as tablets for oral administration. Participants will be instructed to take (or their representatives to administer) their assigned dose of the study intervention orally each day in combination with an investigator-selected background regimen for 48 weeks.

The 25-mg tablets should be taken as a whole, and cannot be chewed, broken, or crushed. CCI [redacted]

Participants who require an RPV dose below 25 mg will start on the 2.5-mg tablet formulation. The tablets must be dispersed prior to use. Their RPV dose will be adjusted according to the final dosing schedule by weight bands as they gain weight. If participants increase in weight such that they require an RPV 25-mg dose, they can change to the 25-mg tablet formulation. The RPV dose will be taken preferably with the main meal of the day, and each dose will be separated by approximately 24 hours.

In participants with a body weight of <25 kg, intensive PK sampling will be performed after 4 weeks of treatment with the RPV dose administered at baseline, or, if applicable, after 2 weeks of treatment with the adjusted RPV dose(s). For practical reasons, the last 3 days before the intensive PK sampling, participants must take the RPV dose in the morning with breakfast. Participants will be confined to the study site in the morning of the intensive PK sampling day and will receive a standard breakfast. Rilpivirine should be taken within 40 minutes following the start of the breakfast. Approximately 2 hours after RPV intake, participants may resume their usual diet. If more practical, participants can switch the RPV intake to another time of the day after the intensive PK sampling, as long as the RPV intake is always with a meal. The meals and dietary restrictions mentioned in Section 5.3, Lifestyle Considerations, should be respected. The exact date and time of the last 2 RPV intakes before the intensive PK visit and of the RPV intake on the intensive PK visit should be recorded in the case report form (CRF), as well as the exact date and time of PK sampling and the start and stop times and content details of the standard breakfast.

For details on background medications, refer to Section 6.5.1. Temporary discontinuation of all ARVs during the study intervention phase will be allowed only in the event of suspected toxicity as described in Section 7.1.1. Criteria for discontinuation of study intervention and participant discontinuation/withdrawal from the study are provided in Section 7.2.

Study intervention administration must be captured in the source documents and the CRF. Study-site personnel will instruct participants and their representatives on how to store study intervention for at-home use as indicated for this protocol (refer to Section 6.2).

Rilpivirine will be manufactured and provided under the responsibility of the sponsor. Refer to latest version of the IB for RPV for a list of excipients.[21] The excipients used in both formulations are safe for administration in the pediatric population participating in the study. Specific detailed dosing and administration instructions will be provided in the pharmacy manual/study-site investigational product and procedures manual, which will be provided before the start of the study. Rilpivirine will be packed in individual, child-resistant participant kits under responsibility of the sponsor. Each kit will contain information and will be labeled as required per Good Manufacturing Practice (GMP) Annex 13 and per local/country regulatory requirements. Labels must remain affixed to the individual participant kit. No medication can be repacked or relabeled without prior approval from the sponsor.

In case a participant missed the RPV intake, and this is noticed within 12 hours of the time of usual intake, the participant should take the missed dose as soon as possible, with food. The participant may then continue his or her usual dosing schedule. In case a participant missed the RPV intake, and it is noticed more than 12 hours after the time of usual intake, the participant should not take that dose and simply resume the usual dosing schedule. The participant should not take a double dose to make up for a missed one. For participants who vomit within 30 minutes after dosing, the dose should be readministered. Redosing is not allowed if the participant vomits more than 30 minutes after dosing.

For a definition of study intervention overdose, refer to Section 8.4, Treatment of Overdose.

6.2 Preparation/Handling/Storage/Accountability

The study intervention must be stored at controlled temperatures ranging from 59°F to 86°F (15°C to 30°C) unless otherwise specified, and in the original packaging. Refer to the pharmacy manual/study-site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage. Study intervention will be administered to the participant by the representative if the participant is deemed unable to self-administer the medication.

Should a deviation in storage conditions occur for RPV, then the study site should refrain from any further dispensation of the affected medication and provide the study-site monitor immediately with the following information:

- Study number
- Reference and batch number(s)
- Kit number
- Study site number
- Temperature log (including date and duration of the deviation, minimum temperature below and/or maximum temperature above the specified range, that the medication was exposed to) and used units (°C or °F)

Deviations in storage conditions will be evaluated by the sponsor and the study site will receive notification whether the affected medication can continue to be used.

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the study intervention accountability form. Participants or their representatives must be instructed to return all original containers, whether empty or containing study intervention. The study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the

participant, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the study intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the study intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants. Returned study intervention must not be dispensed again, even to the same participant. Whenever a participant brings his or her study intervention to the study site for pill count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is a single-arm study, randomization is not applicable.

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

6.4 Study Intervention Compliance

Study-site personnel will maintain a log of all study intervention received. Study intervention supplies for each participant will be inventoried and accounted for.

Compliance to RPV and the background ARVs will be assessed by the PENTA adherence questionnaire (refer to Section 8.10.3 for more information). Compliance to RPV will also be assessed via pill count (study intervention accountability), as documented on the study intervention accountability form. If a participant's intake of study intervention or background ARVs is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

To optimize compliance to both RPV and the background ARVs, adherence counseling should be planned by the investigator/study-site personnel with the participant and his or her representative at the screening visit to discuss the individual issues that may affect each participant's chances of successfully adhering to treatment. Counseling should address the implications of suboptimal adherence for each participant. At the baseline visit, a second adherence counseling session should take place and clear instructions need to be given regarding regimen intake. A compliance check (eg, review of the PENTA adherence questionnaire or study intervention accountability) and additional treatment adherence counseling should take place at every subsequent study visit.

The representative of participants scheduled for an intensive PK visit, and participants as well if appropriate, will also have to complete a diary documenting RPV intake from the start of study treatment until the intensive PK visit (refer to Section 8.10.2 for more information). Participants and/or their representatives should also be contacted via telephone or email to assess compliance (to study intervention and background ARVs) and to reinforce study instructions every day for at

least 3 consecutive days before the intensive PK visit. If the participant has missed a dose of RPV within 10 days before the intensive PK visit, the visit should be rescheduled to allow steady state of RPV to be reached.

6.5 Concomitant Therapy

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) continued at the start of the study or started during the study and different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy, duration of use, dose regimen, route of administration, and indication. Any change in dosages of the non-ARV medication must also be reported in the CRF. Data on concomitant therapies will be collected up to the last study-related activity, even after participant withdrawal (except in case of withdrawal of consent/assent).

For any concomitant therapy given as treatment for a new condition or a worsening of an existing condition occurring after signing the ICF, the condition must be documented in the AE section of the CRF.

6.5.1 Background Regimen

The investigator-selected ARVs, including but not limited to N(t)RTIs (eg, AZT, ABC, TAF, or TDF in combination with FTC or 3TC), whichever are approved and marketed or considered local standard of care for children aged ≥2 to <12 years in a particular country, will be given as the coformulation or as the separate components according to local availability and use in the country (eg, Combivir® or 3TC/AZT, Epzicom®/Kivexa® or ABC/3TC, Truvada® or FTC/TDF). Integrase inhibitors (eg, DTG or raltegravir) can also be administered in combination with RPV, as appropriate. Protease inhibitors and ARVs requiring a PK booster, are disallowed from baseline onwards. No dual combination of ARVs are allowed in this study.

Only branded versions of the background ARVs or generics with tentative United States FDA approval or World Health Organization [WHO] prequalified drugs will be prescribed by the investigator and reimbursed by the sponsor during the 48-week intervention phase. If these are not available, generic drugs approved by the local health authorities or procured by the United Nations (UN) international organizations (eg, United Nations International Children's Emergency Fund [UNICEF]) can be allowed upon approval by the sponsor.

The selected background ARVs will be used in doses that are specified in the individual package inserts or for which sufficient supporting data are available for use in this age group. Applicable procedures and guidance based on package inserts should be respected (eg, in case of missed doses). The intake of the background ARVs will be according to the locally applicable procedures and package inserts, but preferably at the same time as RPV for ARVs with a once daily regimen. For ARVs with a twice daily regimen, one of the doses will be preferably taken together with RPV and the other dose will be taken according to the package insert. All ARVs should be started on the same day (ie, Day 1). For storage conditions of background ARVs, consult the respective package inserts.

Temporary discontinuation of all ARVs during the study intervention phase will be allowed only in the event of suspected toxicity as described in Section 7.1.1.

For those participants who do not tolerate the selected background ARVs, switching to alternative ARVs (branded versions or generics with tentative United States FDA approval and/or WHO prequalified drugs, or if not available, generic drugs approved by the local health authorities or procured by the UN international organizations upon approval by the sponsor) is allowed for some predefined toxicities.

A change of background regimen will be allowed in case the following AEs are reported and preferably after written approval from the sponsor:

- Lactic acidosis
- Hepatotoxicity, including severe hepatomegaly and steatosis even in the absence of marked transaminase elevations
- Renal impairment
- Anemia
- Hypersensitivity reactions

The symptoms of intolerance to the background ARV(s) should be reported as AEs and should be clearly documented as leading to the change in ARV(s).

Special considerations may be warranted for the discontinuation of certain ARVs:

- When discontinuing ART for any reason, please take the following into consideration: NNRTIs, including RPV, have a long plasma elimination half-life compared to N(t)RTIs. In presentations and publications, it has been hypothesized that this difference in elimination half-life of ARVs when stopping therapy may lead to NNRTI resistance.[26,31] Some experts recommend stopping the NNRTI first, before the other ARVs (ie, the N[t]RTI background regimen). Currently, however, there is no consensus on the approach to this issue either among the scientific community or in treatment guidelines.
- Discontinuation of 3TC in patients with hepatitis B co-infection: severe acute exacerbations of hepatitis have been reported after discontinuation of 3TC in patients with chronic hepatitis B infection who are using this agent in their ARV regimen. Discontinuation of this agent for any reason in participants with chronic hepatitis B infection should be undertaken with caution. Careful clinical and laboratory assessment of hepatic status should be undertaken for at least several months in such participants. Initiation of specific anti-hepatitis B therapy may be required (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities).

! Participants who develop a clinically suspected hypersensitivity reaction related to ABC treatment must discontinue ABC treatment immediately. If a hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (Ziagen®, Trizivir®, or Epzicom/Kivexa) should be restarted. Restarting any ABC-containing product following a hypersensitivity reaction results in a prompt return of symptoms within hours. This recurrence of the hypersensitivity reaction may be more severe than on initial presentation, and may include life-threatening hypotension and death (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities).

6.5.2 Allowed Concomitant Therapy

For coadministered therapies, the package insert should be consulted and reviewed carefully. The determinations listed in the respective Contraindications and Warnings and Precautions sections must be respected to prevent any potentially serious or life-threatening drug interactions.

! Investigator-selected background ARVs must be taken during the study.

! H_2-receptor antagonists (eg, famotidine, ranitidine, and nizatidine) should only be administered either at least 12 hours before or at least 4 hours after RPV intake.

! Antacids should only be administered either at least 2 hours before or at least 4 hours after RPV intake.

! If azole treatment or intake of medications associated with a risk of TdP are planned for > 2 days, participants are subjected to additional safety monitoring: an ECG assessment taken 3 to 7 days after start of comedication intake at C_{max}, ie, 4 hours after RPV intake. A PK sample should be taken within 10 minutes after the ECG assessment.

! All medications labeled as having a CYP3A4 inhibitory effect should be used with caution during the study (refer to Section 6.5.3 for disallowed usage). Additional safety monitoring is required in case of >2 days intake, as specified above.

6.5.3 Disallowed Concomitant Therapy

! All investigational drugs (except RPV) and all investigational vaccines are disallowed from 90 days before the baseline visit until the Week 48/Withdrawal visit.

! The following therapies are disallowed from 4 weeks before the baseline visit until the Week 48/Withdrawal visit:

  # Drugs that can potentiate the activity of ARVs or have intrinsic ARV activity (but no indication for treatment of HIV infection): mycophenolic acid, hydroxyurea, hydroxychloroquine, foscarnet.

  # All disallowed medication as mentioned in the package insert of the ARV regimen.

  # Systemic chronic steroids.

! The following anti-HIV therapies are disallowed from baseline onwards:

  # Protease inhibitors.

  # Antiretrovirals requiring a PK booster (eg, elvitegravir).

  # NNRTIs (except for RPV).

- # Fusion inhibitors.
- # C-C chemokine receptor type 5 inhibitors.
- # Generic ARVs not tentatively approved by United States FDA, not prequalified by WHO, not approved by local health authorities, or not procured by UN international organizations (eg, UNICEF).

! Approved vaccines are disallowed within 4 weeks before baseline, and within 4 weeks before a sample for plasma viral load measurement is taken.

! The following therapies are disallowed from screening onwards:

- # All therapies labeled as having a potent CYP3A4 inducing effect (except for the ARVs efavirenz and nevirapine), as coadministration of RPV with these agents may result in decreased RPV plasma concentrations and loss of therapeutic effect. Examples include, but are not limited to, phenobarbital, carbamazepine, oxcarbazepine, phenytoin, modafinil, pioglitazone, troglitazone, rifabutin, rifampin, rifapentine, dexamethasone (more than a single dose), and St. John's wort.
- # Proton pump inhibitors.
- # Tuberculosis treatment with rifamycins.

! Chronic inhaled steroids used concomitantly with intranasal steroids are disallowed within 30 days before baseline and within 30 days before ACTH stimulation testing.

! For participants scheduled for an intensive PK visit, all medications labeled as having a CYP3A4 inhibitory effect are disallowed until the last PK sample at the intensive PK visit has been taken, as coadministration of RPV with these agents may result in increased RPV plasma concentrations. Examples include, but are not limited to, ketoconazole, clarithromycin, erythromycin, roxithromycin, telithromycin, troleandomycin, and aprepitant. Alternative medications without CYP3A4 inhibitory effect should always be considered as the preferred option.

For details on drug interactions with RPV and specific disallowed medication, please consult Section 10.6, Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV.

For contraindicated therapies or therapies that are not recommended for concomitant use with the background regimen, the package inserts of the background ARVs should be consulted.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.6 Dose Modification

6.6.1 Dose Evaluation Criteria

In participants with a body weight of <25 kg, intensive PK sampling will be done to further evaluate the most appropriate RPV dose for participants with a low body weight. Overall across studies TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥10 kg) and C213 (Cohort 2; children aged ≥6 to <12 years), approximately 40 participants will be enrolled of which

at least 12 participants with a body weight of <25 kg at baseline, including at least 7 participants with a body weight of <20 kg at baseline. To accommodate overall regulatory requirements concerning the evaluation of RPV in the pediatric population, the intensive PK data from this study TMC278HTX2002 will be combined with the data from study C213 Cohort 2. For this study, AUC_{24h} of a selected RPV dose under fed and steady-state conditions will be the primary PK parameter for determination of the acceptability of the RPV dose, but the C_{max} and C_{0h}/C_{24h} of RPV will also be taken into consideration.

Dose Evaluation in the Mini-cohort

When reviewing the results of the participants in the mini-cohort, the following evaluation criterion will be taken into account:

- If none of the participants on a given RPV dose has experienced a life-threatening AE (including death) or a grade 4 AE that is at least probably related to RPV, and ≤25% of all participants (ie, at most 1 participant) on a given RPV dose terminated the study intervention due to a grade 3 or grade 4 AE that is at least possibly related to RPV, the RPV dose has passed the safety review.
- If ≤1 of the participants in the mini-cohort has an RPV AUC_{24h} greater than the 90th percentile of adult values (3,513 ng•h/mL) and there are no safety concerns, the mini-cohort has passed the pharmacokinetic review. In case of failure, the starting dose and the expected distribution of RPV C_{0h}, C_{max} and AUC_{24h} will be reviewed and an assessment will be made whether an RPV dose adjustment for participants under e.g., a certain body weight is warranted.

If the RPV dose has not passed the review, the sponsor and IDMC will evaluate whether it is safe to continue finding an optimal RPV dose in these participants (refer to Section 6.6.2).

Dose Evaluation in at least 12 Participants

When reviewing the results of at least 12 participants with a body weight of <25 kg, the following evaluation criteria will be taken into account:

- If none of the participants on a given RPV dose has experienced a life-threatening AE (including death) or a grade 4 AE that is at least probably related to RPV, and ≤25% of all participants on a given RPV dose terminated the study intervention due to a grade 3 or grade 4 AE that is at least possibly related to RPV, the RPV dose has passed the safety review.
- If the geometric mean AUC_{24h} for RPV is between 80% and 150% of the observed geometric mean AUC_{24h} for RPV in HIV-1-infected adults from the Phase 3 PK substudies of C209 and C215 (ie, between 1,426 and 2,673 ng.h/mL)[3], then the RPV dose has passed the PK review.

  Note: If an individual C_{max} is >440 ng/mL (1.85-fold the mean C_{max} of RPV 25 mg once daily in healthy adults, and evaluated as not posing an increased risk for QT interval prolongation), the RPV dose can be continued if there are no safety findings based on an overall assessment of the participant's safety (eg, additional ECG with optional PK sample).

If the RPV dose has not passed the safety and/or PK review, the sponsor and IDMC will evaluate whether it is safe to continue finding an optimal RPV dose in these participants (refer to Section 6.6.2).

6.6.2 Dose Modification (Adjustment) Rules

Dose adjustment will only be considered if exposure (too high or too low) or results would show a safety or efficacy concern that could potentially be avoided by altering the RPV dose. The decision to modify the RPV dose for a specific group of participants will be made by the sponsor upon IDMC recommendation, based on review of all available data (including intensive PK data) after 4 weeks of study treatment.

If an adjusted RPV dose is needed, CCI [redacted] The new dose scheme and clear instructions on how to handle dosing will be provided to all participating sites by the sponsor via a written notification.

The body weight of all participants (**not** limited to participants with a body weight of <25 kg) will be measured at all scheduled visits (refer to the Schedule of Activities), and the dose may be adapted if the participant's body weight changes such that it crosses into a new weight band for which a different RPV dose is recommended. To avoid multiple RPV dose changes based on fluctuations in body weight during the study, individual RPV dose adjustments for changes in weight band should be implemented only for increase in body weight to ≥25 kg (switch to 25 mg RPV dose) or decrease in body weight to < 22.5 kg (switch to 15 mg RPV dose) or decrease in body weight to <18 kg (switch to 12.5 mg). Appropriateness of these doses will be further evaluated in this study in combination with data generated from pediatric study C213. In case of persistent weight loss > 10% of baseline (or of the previous weight leading to a dose change during the study), clinical evaluation should be performed to rule out an underlying condition prior to proceeding to change the RPV dose. Dose change is not allowed between baseline (when weight is defined) and Week 4 (start of intensive PK sampling). Any dose/dosage adjustment should be overseen by medically-qualified study-site personnel (principal or subinvestigator). The RPV dose will not exceed the approved and marketed adult 25-mg dose. Dose adjustment based on changes in body weight does not require intensive PK sampling.

6.7 Intervention After the End of the Study

Upon study completion, participants who continue to experience clinical benefit from treatment with RPV will be offered the opportunity to continue study treatment in the pediatric rollover study TMC278IFD3004 or to 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.

Participants who do not roll over in the pediatric study TMC278IFD3004 will be informed that study intervention will not be made available to them after they have completed/discontinued the study intervention phase and that they should return to their primary physician to determine standard of care.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

The criteria for permanent discontinuation of study intervention are included in Section 7.2, Participant Discontinuation/Withdrawal From the Study. In case a permanent discontinuation of study intervention is needed, ART (ie, RPV and background regimen) should be discontinued.

The guidance on temporary discontinuation and rechallenge is provided below.

7.1.1 Temporary Discontinuation

Temporary discontinuation of all ARVs (RPV or investigator-selected background regimen) during the intervention phase will be allowed in the event of suspected toxicity, as long as the temporary discontinuation is associated with and can be linked to an AE or an SAE. The instructions for temporary discontinuation in case of specific toxicities are provided in Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities.

The maximum allowed duration of a single temporary discontinuation for toxicity reasons will be 4 weeks and the maximum allowed cumulative duration of the temporary discontinuation for toxicity reasons will be 8 weeks. Participants should maintain the regular visit schedule during the temporary discontinuation(s). Additional unscheduled visits may be performed for safety or tolerability reasons. A participant may be withdrawn from the study if the maximum allowed durations mentioned before have been exceeded.

7.1.2 Rechallenge

Rechallenge instructions in case of specific toxicities are provided in Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities.

7.2 Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent/assent.
- Death.
- Failure to comply with the protocol requirements or to cooperate with the study-site personnel.
- Permanent discontinuation of study intervention for any reason. A participant's study intervention will be automatically discontinued if:
  - The investigator or sponsor believes (eg, that for safety or tolerability reasons [eg, AE]) it is in the best interest of the participant to discontinue study intervention.
  - The participant becomes pregnant (refer to Section 10.4, Appendix 4, Contraceptive and Barrier Guidance and Collection of Pregnancy Information).

- # The participant meets at least 1 of the specific toxicities that require permanent discontinuation of study intervention as mentioned in the toxicity management section (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities).
- # The participant experiences a grade 3/4 decrease in serum magnesium (refer to Section 10.5, Appendix 5, DAIDS Table).

! Confirmed prolongation of QTcF or QTcB >500 ms or a confirmed increase in QTcF or QTcB of ≥60 ms from baseline while receiving CYP3A4 inhibitory comedication or medication associated with a risk of TdP, and the QTcF or QTcB values are not normalized approximately 1 week after the comedication treatment was stopped or if comedication treatment cannot be stopped (refer to Section 6.5, Concomitant Therapy).

! Resistance observation at the time of confirmed virologic failure (defined as 2 consecutive plasma viral load measurements ≥200 HIV-1 RNA copies/mL).

! Develops tuberculosis during the study.

! Diagnosed with acute hepatitis A, B, or C infection after baseline.

! Action as per IDMC recommendation in case results of the intensive PK data analysis and the 4-week safety, tolerability, and efficacy data review are deemed unsatisfactory by the sponsor upon IDMC recommendation.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source documents. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Additional participants will be entered to aim for at least 12 participants with intensive PK data (in the current study and study C213 combined). Additional participants may also be recruited upon request of the sponsor if the interpretation of the PK data is hampered (eg, poor study intervention adherence before PK sampling).

If a participant discontinues study intervention and withdraws from the study before the end of the study intervention phase, Week 48/Withdrawal visit and 4-week follow-up visit assessments should be obtained. If the reason for study withdrawal is withdrawal of consent/assent then no additional assessments are allowed.

Withdrawal From the Use of Samples in Future Research

The participant and/or his or her representative may withdraw consent/assent for use of samples for research (refer to Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

7.3 Lost to Follow-up

If a participant is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. Refer to Section 7.2, Participant Discontinuation/Withdrawal From the Study.

8 STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of PK, safety, tolerability, efficacy, and other measurements applicable to this study.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECG, vital signs, blood sampling. Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documents and CRF.

Additional serum or urine pregnancy tests may be performed for girls of childbearing potential, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during participation in the study and 4 weeks after the last dose of study intervention. At screening, contraceptive counseling will be given as appropriate by participant's age.

The total blood volume to be collected from participants will be approximately:

- 200 mL for participants of ≥2 to <6 years of age with a body weight of < 25 kg
- 224 mL for participants of ≥6 to <12 years of age with a body weight of < 25 kg
- 225 mL for participants of ≥6 to <12 years of age with a body weight of ≥ 25 kg

From each participant scheduled for an intensive PK visit, an additional blood volume of approximately 10 mL will be collected on the day of the visit (refer to Section 1.3.2, Schedule of Activities for Intensive Pharmacokinetic Sampling). From each participant requiring an ACTH stimulation test, an additional 4.4 mL will be collected (refer to Section 1.3.1 General Schedule of Activities). For each RPV dose modification as per IDMC analysis (if applicable), if the post dose switch visit is not done within 1 week of the next scheduled visit as indicated in the General Schedule of Activities (refer to Section 1.3.3, Schedule of Activities for Switch to Adjusted RPV Dose [if Applicable]), an additional blood volume of approximately 38.4 mL will be collected (including the blood volume collected during the intensive PK visit).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Time Windows

All study visits should be scheduled relative to the baseline visit date (eg, Day 1 +14 days for Week 2). The study intervention phase should be 48 weeks. The following time windows are recommended:

- For the Week 2 visit (including Week 2 post-switch): ±2 days

- For the Week 4 visit (including Week 4 post-switch):
  - For participants who are enrolled for intensive PK sampling: between Days 28 and 32
  - For all other participants: ±2 days
- For the Weeks 8, 12, 16, 24, 32, 40, and 48 visits: ±1 week
- For the 4-week follow-up visit: ±4 days

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (≤1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent) or sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Use of local anesthetic creams is allowed to minimize the pain during the blood draw. Use of indwelling catheters is encouraged for the intensive PK visit to minimize discomfort and distress due to repeated venipunctures for blood sampling.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual. Samples for bioanalysis should be protected from light during sample processing and storage.

Study-specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy manual/study-site investigational product
- Investigational product preparation and administration instructions for participants' representative
- Laboratory manual
- Electronic data capture (eDC) manual
- Central ECG machine and ECG manual
- Any other manual, as applicable
- Sample ICF and assent form
- Participant diaries

- Study Adherence Questionnaire for Carers/Children
- Palatability Questionnaire
- Swallowability Questionnaire for Participant/Observer
- Contact Information page(s)
- Participation card
- Warning card for ABC hypersensitivity
- Recruitment and enrollment tools

8.1 Efficacy Assessments

At the time points specified in the Schedule of Activities, blood samples for the determination of plasma HIV-1 RNA viral load to assess antiviral activity and samples for the determination of $CD4^+$ cell counts (absolute and percentage relative to total lymphocytes) will be taken.

Plasma viral load levels will be measured at a central lab using a standardized HIV-1 viral load assay as the concentration of HIV-1 RNA in plasma. $CD4^+$ cell counts will be measured at a central lab via flow cytometry. Specimen preparation procedures will be defined in the laboratory manual.

Changes from baseline in plasma viral load or in $CD4^+$ cell counts (either increases or decreases) will not be reported as (S)AEs.

8.2 Safety Assessments

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity. Details regarding the IDMC are provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.8, Appendix 8, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting. Adverse events of interest are based on their relevance in the target population, their known association with other ARVs, and/or their potential importance demonstrated by nonclinical and clinical data with RPV, and include endocrine events of interest, potential QTc interval prolonging events of interest, hepatic events of interest, neuropsychiatric events of interest, and skin events of interest.

Any clinically relevant changes occurring during the study must be recorded in the AE section of the CRF. For participants who do not roll over in the pediatric study TMC278IFD3004, any clinically significant abnormalities persisting at the last study visit will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities:

8.2.1 Physical Examination

To evaluate the participant's eligibility, a full physical examination will be performed at screening. In addition, a full physical examination will be performed at the time points shown in the Schedule of Activities. This examination includes general appearance, eyes, ears, nose and throat, skin and mucous membranes (with particular attention to hyperpigmentation and hirsutism), lymph nodes, respiratory system, cardiovascular system, gastrointestinal system, central nervous system (CNS), peripheral nervous system, musculoskeletal system, and genitourinary system.

At several time points shown in the Schedule of Activities, only a brief physical examination will be performed. These assessments include general appearance, eyes, ears, nose and throat, skin and mucous membranes (with particular attention to hyperpigmentation and hirsutism), lymph nodes, respiratory system, cardiovascular system, gastrointestinal system, and CNS.

At Week 2, only a skin examination will take place.

Examinations do not include rectal or vaginal examination, unless clinically indicated.

Body weight and height will be recorded at the visits specified in the Schedule of Activities. Growth parameter(s), including weight and height (measured by a calibrated stadiometer appropriate for participants aged ≥2 years) will be followed regularly and evaluated consistently using standardized growth charts (refer to Section 10.15).[2] Participants must be lightly clothed and barefoot to obtain body weight, and barefoot to measure their height. The same weighing scale and stadiometer will preferably be used at each visit. Body weight measurements may be used for dose adjustments, if applicable (refer to Section 6.6, Dose Modification).

The assessment of pubertal development will be performed by a modified Tanner assessment consisting of a discrete visual inspection and comparison to the illustrated Tanner scales (refer to Section 10.9, Appendix 9, Tanner Scales).[18] Tanner staging is limited to participants aged ≥6 to <12 years (including participants who turn 12 years old during the study) and will be performed at the time points shown in the Schedule of Activities. For girls, it will be assessed at screening whether they already have had their first menses. For girls who have not yet had their first menses, the occurrence of the first menses will be checked at every visit as part of the evaluation of pubertal development.

8.2.2 Vital Signs

Pulse rate and blood pressure (systolic and diastolic) will be assessed at the time points specified in the Schedule of Activities, and should be performed before blood sampling. Blood pressure and pulse rate measurements will be assessed standing and supine with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiogram

Single ECGs will be collected at the time points specified in the Schedule of Activities, and read by a central ECG vendor. Whenever possible, the ECG should be taken around the expected C_{max} (ie, 4 hours after RPV intake). Additional ECGs must be performed in case of start of certain concomitant medications (refer to Section 6.5.2).

Instructions for the collection (eg, equipment and lead placement), transmission, and archiving of ECGs will be described in the ECG manual provided by the central ECG vendor. The turnaround time for safety alerts from the central ECG vendor to the study site is approximately 72 hours.

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television and cell phones). Participants can be accompanied by their representatives, if needed. Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood sampling.

Two ECG reports will be generated by the central ECG vendor: a preliminary report and a final report. The final report will be reviewed by a board certified (if applicable) cardiologist from the central ECG vendor. Both reports will need to be interpreted for clinical significance, signed, and dated by the investigator, and filed in the participant's medical record.

8.2.4 Clinical Safety Laboratory Assessments

Blood samples for biochemistry, hematology, and endocrinology (only for participants aged ≥6 to <12 years, including participants who turn 12 years old during the study), and a random urine sample for urinalysis will be collected as noted in Section 10.7, Appendix 7, Clinical Laboratory Tests at the time points specified in the Schedule of Activities. The investigator must review the laboratory results generated by the central laboratory, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

The participants need to have fasted overnight (for at least 10 hours) before the biochemistry safety blood samples are drawn. Samples that were taken under nonfasted conditions and that reveal values that are outside the normal ranges and deemed clinically relevant for parameters that are affected by food intake should be retested after the participant has fasted overnight. In case of early withdrawal, safety blood samples may be taken at the time of dropout, even if the participant has not fasted for at least 10 hours.

The central laboratory will send the investigator an alert form whenever a grade 3/4 laboratory abnormality has been observed (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities). In case a grade 3/4 laboratory abnormality occurs, a confirmatory test should be performed, preferably within 48 hours (if practically feasible) but no later than 72 hours after the results have become available.

The following laboratory abnormalities do not warrant mandatory confirmation within 48 hours:

- asymptomatic grade 3/4 glucose or triglyceride elevations, or asymptomatic grade 3 cholesterol elevations.
- asymptomatic grade 3 pancreatic amylase elevations in participants with no history or concomitant disease of pancreatitis.

8.2.5 Behavior Risk Monitoring

There have been reports of depression when RPV has been given to some participants with HIV-1 infection (refer to Section 2.3.3, Known Risks), as noted in the product label. The sponsor considers it important to monitor for such events during this clinical study.

Participants treated with RPV should be monitored appropriately and observed closely for depression or any other unusual changes in behavior. Consideration should be given to discontinuing RPV in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants treated with RPV must be instructed to monitor participants for the emergence of depression and unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Depression will be assessed at the time points specified in the Schedule of Activities using questionnaires or other means (as available at the site) as part of local standard of care, to determine who needs to be referred for a complete mental health assessment by a mental health professional. Any clinically relevant changes occurring during the study will be reported as AEs.

Also, if the study-site personnel feels that the participant has under-reported his or her symptoms, or if depression or suicidal ideation or behavior are suspected, the participant should be referred for a complete mental health assessment.

8.3 Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant and/or his or her representative for the duration of the study.

Clinically significant changes in laboratory values, other diagnostic tests (except in case of changes in resistance pattern, plasma viral load, and $CD4^+$ cell counts), and intercurrent illnesses will be reported as AEs.

Anticipated events will not be recorded and reported as this is the first study that includes participants aged <6 years. Additionally, no SAEs are anticipated in a stable HIV-1-infected pediatric population aged ≥2 to <12 years. All SAEs are important in understanding the safety of the product.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.8, Appendix 8, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

During the entire study period, including screening and follow-up phases, specific toxicities will be monitored. A safety plan will be followed in case of specific toxicities (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant and representative is the preferred method to inquire about AE occurrence.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.8, Appendix 8, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.5 Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the SAE Form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6 HIV-related Events and HIV-related Outcomes

The events or outcomes listed in the Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report[1] will be recorded as HIV-related events (including AIDS-defining illnesses and Stage-3-defining Opportunistic Illnesses in HIV Infection) in the AE section of the CRF.

All HIV-related events will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure.

8.4 Treatment of Overdose

For this study, any dose of RPV greater than the assigned dose within the protocol-specified interval (refer to Study Interventions Administered in Section 6.1) will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and ECG abnormalities.
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 Pharmacokinetics

Blood samples will be used to evaluate the plasma PK of RPV. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.5.1 Evaluations

Venous blood samples of approximately 1 mL will be collected for measurement of plasma concentrations of RPV at the time points specified in the Schedule of Activities. When additional safety monitoring ECGs are performed in case of start of certain comedications (refer to Section 6.5.2, Allowed Concomitant Therapy), a PK sample should be taken within 10 minutes after each of these ECGs to assess the impact of the comedication on the RPV plasma levels and to evaluate the RPV concentration-safety relationship, if feasible.

The exact date and time of blood sampling and of the last 2 RPV intakes before blood sampling must be recorded in the CRF. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.5.2 Analytical Procedures

Plasma PK samples will be analyzed to determine concentrations of RPV using a validated, specific, and sensitive liquid chromatography – mass spectrometry/mass spectrometry method by or under the supervision of the sponsor.

If needed, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of other coadministered treatments, protein binding, and the metabolite profile.

8.5.3 Pharmacokinetic Parameters and Evaluations

Intensive Pharmacokinetics

Based on the individual plasma concentration-time data, using the actual dose taken and the actual PK sampling times, the following PK parameters of RPV will be derived:

C_{0h}, C_{24h}, C_{min}, C_{max}, $C_{ss,av}$, t_{max}, AUC_{24h}, CL/F, V_{ss}/F, and FI

Other PK parameters may be estimated for exploration of the data, as appropriate.

For the PK parameters, definitions and methods of calculation are:

C_{0h}:	predose plasma concentration
C_{24h}	plasma concentration at 24 hours postdose
C_{min}:	minimum observed plasma concentration
C_{max}:	maximum observed plasma concentration
$C_{ss,av}$:	average plasma concentration at steady state
t_{max}:	time to reach the maximum observed plasma concentration
AUC_{24h}:	area under the plasma concentration-time curve from time of administration up to 24 hours postdose
CL/F:	total apparent clearance at steady state, calculated by dose/AUC_{24h}
V_{SS}/F:	apparent volume of distribution at steady state
FI:	fluctuation index

CCI

[redacted]

8.6 Pharmacokinetic/Pharmacodynamic Evaluations

Pharmacokinetic/PD evaluations will be performed to explore the relationship between PK and safety/efficacy variables.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in the current study.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10 Other Assessments

8.10.1 Resistance

At time points specified in the Schedule of Activities, samples for the determination of viral genotype will be taken. Viral genotyping will be performed centrally by a qualified provider using automated population-based dideoxynucleotide sequencing of the HIV-1 regions of interest. Genotyping of HIV-1 will only be initiated when the plasma viral load is sufficiently high. Changes in viral genotype will not be regarded as (S)AEs.

In addition, a PBMC sample will be taken to allow retrospective characterization of archived viral resistance, if needed. No human DNA analysis will be performed on these samples.

Deep sequencing and viral phenotyping may be performed retrospectively considering the amounts of plasma available after standard genotypic resistance testing.

8.10.2 Diaries

Participants scheduled for an intensive PK visit and/or their representatives will have to complete a diary (provided at baseline or at start of treatment with an adjusted dose) documenting RPV intake from the start of study treatment at baseline or at start of treatment with an adjusted dose until the day of intensive PK sampling. Study-site personnel will instruct the participants and/or their representatives to capture the data according to the study design and not to wait until the study-site visit to record information. For RPV intakes and accompanying meals at home, participants and/or their representatives will be asked to note the exact times of RPV intakes and accompanying meals (stop times).

The investigator or study-site personnel should review the recorded data in the participant's diary. Upon diary completion and review, the results of the diaries will be transcribed into the CRF by the study-site personnel.

8.10.3 Questionnaires

Questionnaires will only be administered if a certified translation is available in the local language. Sites should always use the most recently provided version of the questionnaire. Depending on the age and literacy of the participant, the questionnaires can be completed by the participant and/or by his or her representative. If a participant and his or her representative have difficulties in completing the questionnaire, then the study-site personnel may assist. Once completed, the study-site personnel should review the questionnaire for completeness. The responses to the questionnaires will be transcribed into the CRF by the study-site personnel.

Treatment Adherence

At all visits indicated in the Schedule of Activities, participant treatment adherence will be assessed by a number of sponsor-selected questions from the PENTA adherence questionnaire (refer to Section 10.10, Appendix 10). Site staff, such as a counselor, should support the participant or their parent(s)/caregiver(s) to complete the questionnaire together, where the participant or their parent(s)/caregiver(s) provides the responses to the counselor.

Palatability

The palatability of the 2.5-mg RPV tablet formulation will be assessed in a palatability questionnaire after a 2-week treatment period by documenting the participant's reaction when he or she is given the medication (refer to Section 10.11, Appendix 11). The palatability questionnaire will include a 5-point hedonic facial scale. This scale is a standard tool used in clinical studies to assess drug palatability in children. The palatability questionnaire will be completed within 5 to 15 minutes after RPV intake.

Swallowability

The swallowability of the RPV 25-mg tablet formulation will be assessed in a swallowability questionnaire after a 2-week treatment period by documenting the participant's reaction when he or she is given the medication (refer to Section 10.12, Appendix 12). The swallowability questionnaire will be completed within 5 to 15 minutes after RPV intake.

9 STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1 Statistical Hypotheses

No formal hypothesis will be tested.

9.2 Sample Size Determination

No formal sample size calculation was performed. The sample size is based on overall regulatory requirements and the number of participants enrolled in Cohort 2 in study C213.[4] As described in Section 4.1, Overall Design, the aim is to recruit approximately 25 to 30 participants aged ≥2 to <12 years in the current study.

The precision of the efficacy parameter (proportion of participants with plasma viral load <50 HIV-1 RNA copies/mL, Snapshot approach) expressed as the 95% confidence interval (CI) is presented in Table 1, assuming a sample size of 25 participants and response rates between 80% and 95%.

Table 1: Clopper Pearson 95% CI (2-Sided) for Various Assumptions

Sample Size (N=25)	Response Rate			
	80% (20/25)	84% (21/25)	88% (23/25)	94% (24/25)
95% CI	(59.3; 93.2)	(63.9; 95.5)	(74.0; 99.0)	(79.6; 99.9)

Related to safety, Table 2 shows the probability of the occurrence of at least 1 SAE for various sample sizes, provided the true incidence is 1%, 5%, and 10%.

Table 2: Probability (%) of at Least 1 SAE Reported for Various Assumptions

Sample Size (N)	True Incidence		
	1%	5%	10%
25	22.2	72.3	92.8
30	26.0	78.5	95.8

In study C213, the observed inter-individual variability on apparent RPV clearance was approximately 32%. With a sample size of 10 participants, there is >80% power to achieve 95% CIs for apparent clearance within 70% and 140% of the geometric mean parameter estimates, even when assuming a higher variability (percentage of) coefficient of variation ([%]CV) of 42%.[38] Thus, at least 12 participants with a body weight of <25 kg are considered to be adequate for characterizing the RPV PK in that group. As recruitment for the entire group may be lengthy, an IDMC analysis will be done after ≥5 participants with a body weight of <25 kg have had their intensive PK visit and 4-week safety.

9.3 Populations for Analyses

All statistical analysis will be performed on the intent-to-treat population, defined as all participants who receive at least 1 dose of RPV.

9.4 Statistical Analyses

The primary analysis (with formal database lock) will be done when all participants have reached Week 24 (or discontinued earlier). The final analysis (with formal database lock) will be done when all participants have reached Week 48 (or discontinued earlier). A detailed SAP for each analysis will be written and signed off prior to database lock.

The results of all analyses up to Week 48 will be shared and discussed with the IDMC.

During the study, IDMC analyses will be performed to monitor PK, safety, tolerability, and efficacy data, and to safeguard the participants in this study (refer to Section 9.5, Independent Data Monitoring Committee Analyses).

9.4.1 Initial Participant and Disease Characteristics

All demographic (eg, age, height, weight, gender, body mass index, and race) and other initial participant characteristics (eg, physical examination, medical and surgical history, and concomitant diseases) will be tabulated and analyzed descriptively.

9.4.2 Efficacy Analyses

Plasma Viral Load

An outcome analysis (ie, proportion of participants with a plasma viral load <50 and <400 HIV-1 RNA copies/mL) will be performed using Snapshot approach. The Snapshot analysis is based on

the last observed plasma viral load data within the visit window (ie, Weeks 24 and 48). The proportion of participants with virologic failure (ie, HIV-1 RNA ≥50 and ≥400 copies/mL) per Snapshot approach will be provided. Participants who switched ARVs for tolerability reasons not allowed per protocol will be considered as virologic failures for this Snapshot approach. Proportions will be expressed as percentages with Clopper Pearson 95% CI at each time point.

$CD4^+$ Cell Count

The analysis will be based on observed values and on imputed values using NC=F, ie, participants who prematurely discontinued the study will have their $CD4^+$ cell count following discontinuation imputed with the baseline value (resulting in a change of 0), and will have last-observation-carried-forward imputation for intermediate missing values.

Actual values and changes from baseline will be descriptively and graphically presented.

9.4.3 Safety Analyses

Adverse Events/HIV-Related Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs (including HIV-related events) are AEs with onset during the intervention phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each treatment-emergent AE/HIV-related event, the percentage of participants who experience at least 1 occurrence of the given event will be tabulated per study phase (ie, screening phase, intervention phase, and follow-up). Separate tabulations will be made by severity and relationship to the study intervention, as appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study intervention due to an AE, or who experience a grade 3/4 AE, an AE of special interest, or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Descriptive statistics include number of observations (n), mean, standard deviation (SD), median, minimum, and maximum.

Frequency tabulations of the changes from baseline will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). For the tests available, laboratory abnormalities will be determined using the DAIDS grading table (refer to Section 10.5, Appendix 5, DAIDS Table). Frequency tabulations of worst abnormality grade after baseline will be generated. As appropriate, frequency tabulations and listings will be provided for participants who develop a grade 3/4 laboratory abnormality.

Descriptive statistics of the actual values and changes from baseline of the endocrine assessments (cortisol, follicle-stimulating hormone [FSH], luteinizing hormone [LH], androstenedione, testosterone, and dehydroepiandrosterone sulfate [DHEAS]) will be generated.

Results of reflex ACTH testing will be listed.

Electrocardiogram

Descriptive statistics of ECG values and changes from baseline will be summarized at each scheduled time point. The ECG parameters analyzed are heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB, and QTcF.[20] Descriptive statistics include number of observations (n), mean, SD, median, minimum, and maximum. Frequency tabulations of the abnormalities will be made. Refer to Section 10.13, Appendix 13, Cardiovascular Safety – Abnormalities, for the definition of the ECG abnormalities.

Vital Signs

Descriptive statistics of pulse rate and blood pressure (systolic and diastolic) (supine and standing) values and changes from baseline will be summarized at each scheduled time point. Descriptive statistics include number of observations (n), mean, SD, median, minimum, and maximum. The percentage of participants with values beyond clinically important limits will be summarized at each time point. Refer to Section 10.13, Appendix 13, Cardiovascular Safety – Abnormalities, for the definition of the vital signs abnormalities.

Physical Examination

Physical examination findings will be summarized at each scheduled time point per body system. Physical examination abnormalities will be listed.

Growth will be followed regularly and evaluated consistently using standardized growth charts. Descriptive statistics of height, height-for-age, weight, weight-for-age, body mass index (BMI), and BMI-for-age will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Descriptive statistics include number of observations (n), mean, SD, median, minimum, and maximum.

Tanner stage (for pubic hair and genitalia/breasts) will be cross-tabulated versus baseline by age. 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.

9.4.4 Pharmacokinetic Analyses

Intensive Pharmacokinetics

Pharmacokinetic and statistical analyses of the results will be done using WinNonlin Professional™ (Pharsight Corporation, Mountain View, California, United States), Microsoft Excel® (Microsoft Redmond, Washington, United States), and SAS (SAS Institute Inc. Cary, NC, United States). A noncompartmental model with extravascular input will be used for the PK analysis.

Data will be listed for all participants with available plasma concentrations. Participants will be excluded from the intensive PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; vomiting; concentration data not sufficient for PK parameter calculation).

Actual sampling times will be checked for major aberrations. In case a major aberration occurs for an actual sampling time (ie, >20% deviation from the scheduled time), this plasma concentration will be excluded from descriptive statistics in the plasma concentration table.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics, including sample size (n), arithmetic mean, SD, (%)CV, geometric mean, median, minimum, and maximum, will be calculated for all individual derived PK parameters of RPV.

For each participant, plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis including various transformations in order to get a general overview.

CCI

[redacted]

CCI

[redacted]

[redacted]

Pharmacokinetic/Pharmacodynamic Analyses

Efficacy and safety parameters will be subjected to a PK/PD analysis. Various efficacy and safety parameters will be linked to the PK of RPV applying graphical tools and, if feasible, statistical models.

9.4.5 Other Analyses

Resistance

Results from viral genotyping in plasma or in proviral DNA (archived resistance), as applicable, 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.

Diaries

A participant listing will be created for participants who are enrolled for intensive PK sampling, with the date and time of RPV intake from the start of study treatment until the day of intensive PK sampling, based on the information entered in the participant diary.

Questionnaires

Treatment Adherence

Participant listings will be created so that adherence can be checked on an individual basis.

Treatment adherence will be summarized based on study intervention accountability as the amount of RPV doses taken versus amount of RPV doses supposed to be taken. Descriptive statistics include number of observations (n), mean, SD, median, minimum, and maximum. In addition, the proportion of participants that are adherent (ie, adherence ≥95%) will be summarized.

The responses to the PENTA adherence questionnaire will be tabulated at each time point (refer to Section 10.10, Appendix 10). Treatment adherence will be further summarized per time point based on a "worst case" combination of results for a number of sponsor-selected questions, categorizing participants into "treatment adherent" and "treatment nonadherent".

Palatability

The responses to the palatability questionnaire will be tabulated.

Swallowability

The responses to the swallowability questionnaire will be tabulated.

9.5 Independent Data Monitoring Committee Analyses

An IDMC will be established to monitor and review PK, safety, tolerability, and efficacy data on an ongoing basis and to ensure the continuing safety of the participants enrolled in this study, as noted in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations. The IDMC will evaluate the appropriateness of the RPV dose for participants with a body weight of <25 kg and will make recommendations regarding the continuation, modification, or termination of the study (refer to Section 4.2, Scientific Rationale for Study Design). The IDMC will be the same committee as for the study C213 and will include at least 1 HIV specialist and at least 1 statistician.

The following analyses will be shared and discussed with the IDMC:

- The analyses (no formal database lock) when participants in the mini-cohort (in the current study and study C213 combined) received at least 4 weeks of treatment with the RPV dose (25 mg, 15 mg, 12.5 mg or another adjusted weight-based dose) (or discontinued earlier).
- The analyses (no formal database lock) when at least 12 participants with a body weight of <25 kg (in the current study and study C213 combined) received at least 4 weeks of treatment with the RPV dose (25 mg, 15 mg, 12.5 mg or another adjusted weight-based dose) (or discontinued earlier).
- The analysis (no formal database lock) when all participants have reached 12 weeks of study treatment (or discontinued earlier).
- The analyses (formal database lock) when all participants have reached 24 (primary analysis) and 48 weeks (final analysis) of study treatment (or discontinued earlier).

Details will be described in the IDMC charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Abbreviations and Trademarks

3TC	lamivudine
ABC	abacavir
ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24h}	area under the plasma concentration-time curve from time of administration up to 24 hours postdose
AZT	azidothymidine
BMI	body mass index
C_{0h}	predose plasma concentration
C_{24h}	plasma concentration at 24 hours postdose
CL/F	total apparent clearance at steady state
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
$C_{ss,av}$	average plasma concentration at steady state
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CNS	central nervous system
CRF	case report form(s) (paper or electronic as appropriate for this study)
CV	coefficient of variation
CYP	cytochrome P450
d4T	stavudine
DAIDS	Division of AIDS
ddI	didanosine
DHEAS	dehydroepiandrosterone sulfate
DNA	deoxyribonucleic acid
DTG	dolutegravir
ECG	electrocardiogram
eDC	electronic data capture
EFV	efavirenz
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FI	fluctuation index
FSH	follicle-stimulating hormone
FTC	emtricitabine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IAS-USA	International Antiviral Society United States of America
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous(ly)
LDL	low-density lipoprotein
LH	luteinizing hormone
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PENTA	Pediatric European Network for the Treatment of AIDS
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAM	resistance-associated mutation
RBC	red blood cell
RNA	ribonucleic acid
RPV	rilpivirine
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TdP	Torsade de Pointes
t_{max}	time to reach the maximum observed plasma concentration
ULN	upper limit of normal
UN	United Nations
UNICEF	United Nations International Children's Emergency Fund
V_{SS}/F	apparent volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WT	wild type

Definitions of Terms

BMI	Body weight (kg) / [height (m)]^2
CL/F	Dose divided by AUC_{24h}
eGFR	k x height (cm) / plasma creatinine (P_{cr}) (mg/dL) with k = 0.55 in children aged 2-12 years, 0.55 in adolescent girls aged 13-21 years, and 0.70 in adolescent boys aged 13-21 years
QTcB	QTcB = QT x $(1000/RR)^b$ where b = 1/2
QTcF	QTcF = QT x $(1000/RR)^b$ where b = 1/3

Virologic Failure	Lack or loss of virologic response
Suspected Virologic Failure	HIV-1 RNA ≥ 200 copies/mL after confirmed HIV-1 RNA of <50 copies/mL
Confirmed Virologic Failure	2 consecutive HIV-1 RNA plasma viral load measurements ≥200 copies/mL

10.2 Appendix 2: Monitoring and Safety for Specific Toxicities

Guidelines in this section are applicable for the entire study period, including the screening and follow-up phases. An overview of the laboratory ranges to assign grading to a laboratory value is provided in Section 10.5, Appendix 5, DAIDS Table.

For grade 3 or 4 laboratory abnormalities, participants should have a confirmatory measurement, preferably within 48 hours after the laboratory results become available to the site. This management scheme is for confirmed laboratory abnormalities and not for isolated events.

The following laboratory abnormalities do not warrant mandatory confirmation within 48 hours:

- Asymptomatic grade 3 or 4 glucose or triglyceride elevations, or asymptomatic grade 3 cholesterol elevations
- Asymptomatic grade 3 pancreatic amylase elevations in participants with no history or concomitant disease of pancreatitis

All grade 3 and grade 4 laboratory abnormalities and laboratory abnormalities resulting in an increase of 2 DAIDS grades from baseline will be followed until return to baseline or within 1 grade from baseline. Certain long-term AEs of ART cannot be followed to resolution within the setting of this study; in these cases, follow-up will be the responsibility of the investigator, which will be agreed upon with the sponsor.

For participants reporting rash, allergic reaction, AST/ALT and total bilirubin elevations, pancreatic amylase/lipase elevations, clinical hepatitis, neuropsychological symptoms, gastrointestinal nausea, diarrhea, signs and symptoms of adrenal insufficiency, or other toxicities the following actions should be taken:

RASH

Participants who have a history of a grade 2 or 3 rash may be at increased risk for RPV-related skin reaction and should therefore be monitored closely during the first 4 weeks of study treatment.

All the information regarding rash occurring after the first intake of study intervention needs to be reported in the Rash section of the CRF within 24 hours and the study site monitor needs to be informed. Rash occurring before the first intake of study intervention is to be reported as AEs (refer to Section 8.3).

Any skin change should be evaluated with specific attention for systemic symptoms, mucosal involvement, laboratory abnormalities (including eosinophilia and increases in ALT/AST), and vital sign changes such as decreases in blood pressure or fever.

In case of rash, safety blood samples need to be taken, which are to be processed by the local laboratory. These samples need to be taken during the unscheduled visits as described below. The following parameters need to be tested: AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin (total, direct, and indirect), creatinine, and a complete blood cell

count (including hemoglobin, hematocrit, red blood cell [RBC] count, white blood cell [WBC] count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

If the etiology of the rash is clear, and is not related to RPV, as in the case of concomitant illness, skin infection, or trauma, standard management should be undertaken. Examples include herpes zoster, cutaneous fungal infections, acne, cuts, or burns. The event should be followed up as an infection/regular AE and be reported on the AE pages of the CRF.

Dermatologist fees for evaluating participants who experience rash will be reimbursed by the sponsor.

Grade 1 Rash

Participants may continue ART and may be treated symptomatically until the rash resolves. Cetirizine (antihistamine), topical corticosteroids, or antipruritic agents may be prescribed. The participant and/or his or her representative should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Referral to a dermatologist is optional.

Participants and/or their representatives should be informed that they should visit the site immediately when they notice any rash. For close follow-up, unscheduled visits will also be performed on 1 and 7 days after occurrence of any rash. If rash is unresolved after 7 days, additional unscheduled visits can be performed at the investigator's discretion until resolution.

Grade 2 Rash

Participants may continue ART. Antiretroviral therapy may also be continued for any grade 2 rash with an increase in ALT/AST (<2x baseline) provided the participant is followed weekly with repeated testing. For participants with a grade 2 rash and elevations of ALT/AST >2x baseline but <5x upper limit of normal (ULN), ART should be interrupted and should only be restarted when the cutaneous reaction has resolved.

The participant and/or his or her representative should be advised to contact the investigator immediately if the rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops. Cetirizine (antihistamine), topical corticosteroids, or antipruritic agents may be prescribed.

Referral to a dermatologist is optional.

Participants and/or their representatives should be informed that they should visit the site immediately when they notice any rash. For close follow-up, unscheduled visits will also be performed on 1 and 7 days after occurrence of any rash. If rash is unresolved after 7 days, additional unscheduled visits can be performed at the investigator's discretion until resolution.

Grade 3 Rash

Participants will permanently discontinue ART and will be withdrawn from the study. No rechallenge is allowed.

A biopsy should be taken within 24 hours (either by the investigator or the dermatologist) and a dermatologist should be consulted as soon as possible, preferably also within 24 hours.

Biopsies will be analyzed locally. The sponsor may have a central analysis performed by a selected pathologist. For this purpose, the local slides may be requested; after analysis, they will be returned to the site.

Participants and/or their representatives should be informed that they should visit the site immediately when they notice any rash. For close follow-up, unscheduled visits will also be performed as follows: daily for the first 5 days after occurrence, weekly until resolution. In addition, extra unscheduled visits can be performed at the investigator's discretion.

If on **day 1** (initial rash evaluation visit, when investigator notices the rash for the first time) there are no increases in ALT/AST noted and there is no progression of rash (eg, rash increases in size or spreads to other parts of the body or additional blisters/vesicles/ulcerations develop) during the first 5 days then safety blood samples should also be taken on Day 5.

If on **day 1** the ALT/AST are ≥2x baseline and ≥5x ULN, then safety blood samples should be taken daily for the first 5 days.

If on **day 5** the ALT/AST are ≥2x baseline and ≥5x ULN, then safety blood samples should be taken at least weekly until resolution of ALT/AST abnormalities.

At the investigator's discretion, ALT/AST can be measured more frequently.

Grade 4 Rash

Participants will permanently discontinue ART and will be withdrawn from the study. No rechallenge is allowed.

A biopsy should be taken within 24 hours (either by the investigator or the dermatologist) and a dermatologist should be consulted as soon as possible, preferably also within 24 hours.

Biopsies will be analyzed locally. The sponsor may have a central analysis performed by a selected pathologist. For this purpose, the local slides may be requested; after analysis, they will be returned to the site.

Participants and/or their representatives should be informed that they should visit the site immediately when they notice any rash. For close follow-up, unscheduled visits will also be performed as follows: daily for the first 5 days after occurrence, weekly until resolution. In addition, extra unscheduled visits can be performed at the investigator's discretion. Participants should be hospitalized whenever medically appropriate for management of grade 4 rashes.

If on **day 1** (initial rash evaluation visit, when investigator notices the rash for the first time) there are no increases in ALT/AST noted and there is no progression of rash (eg, rash increases in size or spreads to other parts of the body or additional blisters/vesicles/ulcerations develop) during the first 5 days then safety blood samples should also be taken on Day 5.

If on **day 1** the ALT/AST levels are ≥2x baseline and ≥5x ULN, then safety blood samples should be taken daily for the first 5 days.

If on **day 5** the ALT/AST levels are ≥2x baseline and ≥5x ULN, then safety blood samples should be taken at least weekly until resolution of ALT/AST abnormalities.

At the investigator's discretion, the ALT/AST levels can be measured more frequently.

Table 3: Summary of Rash

DAIDS Toxicity Grade	Investigator Action	Rechallenge Instructions
Grade 1	May continue ART	NA
Grade 2	May continue ART	NA
Grade 3	Discontinue ART	No
Grade 4	Discontinue ART	No

NA=not applicable

ACUTE SYSTEMIC ALLERGIC REACTION

Management will be at the discretion of the investigator, taking into account the following protocol-defined procedures, and should follow generally accepted medical standards.

Participants with ABC in their background regimen and developing an acute systemic allergic reaction should be evaluated for the possibility of ABC hypersensitivity reaction and follow the instructions related to clinically suspected hypersensitivity to ABC (refer to Hypersensitivity Reactions).

Grade 1 Acute Systemic Allergic Reaction

Participants may continue ART. The participant and/or his or her representative should be advised to contact the investigator immediately if there is any worsening of the localized urticaria, or if any systemic signs or symptoms develop.

Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed as long as these are in line with the package inserts of the background ARVs or the (dis)allowed medication for RPV as indicated in Section 6.5.

Grade 2 Acute Systemic Allergic Reaction

Participants may continue ART. If there is any worsening of the allergic reaction, the participant and/or his or her representative should be advised to contact the investigator immediately, ART will be discontinued and the participant will be withdrawn from the study.

Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed as long as these are in line with the package inserts of the background ARVs or the (dis)allowed medication for RPV as indicated in Section 6.5.

Grade 3 and **Grade 4 Acute Systemic Allergic Reaction**

Participants will permanently discontinue ART and will be withdrawn from the study (refer to Section 7). Participants will be treated as clinically appropriate. Standard management should be undertaken.

AST, ALT, AND TOTAL BILIRUBIN ELEVATION

Management will be at the discretion of the investigator, taking into account the following protocol-defined procedures (also refer to Table 4), and should follow generally-accepted medical standards. This management scheme is for confirmed laboratory abnormalities and not for isolated events.

Grade 1 AST or ALT Elevation and Grade 2 AST or ALT Elevation with Grade 1 or 2 Total Bilirubin Elevation

Participants may continue ART.

Grade 3 AST or ALT Elevation with Grade 1 or 2 Total Bilirubin Elevation

Participants are to interrupt ART, except if they are co-infected with hepatitis A, B, or C (see below). Upon resolution of the laboratory abnormality to at least the lower grade level (at most grade 2), the participant may resume ART under the guidance of the investigator and preferably after the investigator has consulted with a sponsor's physician.

If a participant is required to interrupt ART due to a grade 3 AST or ALT elevation, and after restarting ART he or she has a recurrence of grade 3 or grade 4 AST or ALT elevation, then he or she will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

For participants with concomitant hepatitis A, B, or C:

Warning: Severe acute exacerbations of hepatitis B have been reported in participants who are co-infected with hepatitis B virus and HIV and have discontinued FTC, TAF, TDF, or 3TC. Hepatic function should be monitored closely in these participants, with both clinical and laboratory follow-up for at least several months. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

If a participant is diagnosed with acute viral hepatitis during the study, then he or she must be withdrawn from the study immediately and the necessary follow-up visits performed (refer to Section 7). Participants with chronic hepatitis B or C co-infection will be allowed to continue ART if they develop a grade 3 elevation in AST or ALT, provided that ALP is not elevated to grade 2 or higher and total bilirubin is not elevated to grade 3 or higher, and they do not have signs and symptoms of clinically active hepatitis. Signs and symptoms of active hepatitis include, but are not limited to, fatigue, malaise, anorexia, nausea, dark urine and clay-colored stools, bilirubinuria,

jaundice, and liver tenderness. If signs or symptoms of clinically active hepatitis occur, or if AST or ALT increases to grade 4, then the participant will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

If a participant co-infected with hepatitis B or C experiences grade 3 elevation in AST or ALT, ART will be interrupted. If after restarting ART, the participant has a recurrence of grade 3 increase in AST or ALT, he or she may continue ART provided that ALP is not elevated to grade 2 or higher and total bilirubin is not elevated to grade 3 or higher, and he or she does not have signs and symptoms of clinically active hepatitis. If signs or symptoms of clinically active hepatitis occur, or if AST or ALT increases to grade 4, then ART will be permanently discontinued and the participant will be withdrawn from the study (refer to Section 7). If for the hepatitis B or C co-infected participant treatment is interrupted a second time because of a grade 3 elevation in AST or ALT, ART will be permanently discontinued and the participant will be withdrawn from the study (refer to Section 7).

Grade 3 AST or ALT Elevation With at Least Grade 3 Total Bilirubin Elevation or Grade 4 AST or ALT Elevation

Participants will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

Table 4: Summary of AST and ALT Elevations

DAIDS Toxicity Grade	Investigator Action	Rechallenge Instructions
Grade 1	May continue ART if total bilirubin is ≤ grade 2	NA
Grade 2	May continue ART if total bilirubin is ≤ grade 2	NA
Grade 3	**If total bilirubin is ≤ grade 2:** Interrupt ART until toxicity ≤ grade 2; If co-infected with hepatitis B or C, ART may be continued if ALP is ≤ grade 2, bilirubin is ≤ grade 3, and asymptomatic.	Allowed once If recurrence after restart of ART, discontinue ART permanently
	If total bilirubin is > grade 2: Discontinue ART (refer to Section 7)	No
Grade 4	Discontinue ART (refer to Section 7)	No

NA=not applicable

PANCREATIC AMYLASE OR LIPASE ELEVATIONS

For confirmed asymptomatic grade 1 and grade 2 pancreatic amylase and/or lipase elevations, and confirmed asymptomatic grade 3 pancreatic amylase elevations with no history or concomitant disease of pancreatitis, participants should be carefully evaluated and followed closely.

For confirmed asymptomatic grade 4 elevations of pancreatic amylase or confirmed asymptomatic grade 3 or grade 4 elevations of lipase, participants should interrupt ART until pancreatic amylase returns to grade ≤3 or lipase returns to grade ≤2, at which time ART could be reintroduced. If after reintroduction of ART asymptomatic grade 4 elevations of pancreatic amylase or asymptomatic grade 3 or 4 lipase levels recur, ART will be permanently discontinued and the participant will be withdrawn from the study (refer to Section 7).

SIGNS AND SYMPTOMS OF ADRENAL INSUFFICIENCY

Clinical signs and symptoms of adrenal insufficiency may include, but are not limited to, tiredness, weakness, mental depression, headache, anorexia, weight loss, dizziness, orthostatic hypotension, abdominal cramps, diarrhea, electrolyte disturbances, hypoglycemia, mild normocytic anemia, lymphocytosis, eosinophilia, loss of body hair in women, hyperpigmentation, and hirsutism. Pigmentation and hirsutism are evaluated at the scheduled physical examinations (refer to Section 1.3).

In case of clinical signs or symptoms, or laboratory abnormalities (other than cortisol) indicative for adrenal insufficiency, an ACTH stimulation test should be done as soon as possible during an unscheduled visit. For additional details about the ACTH stimulation test and other endocrine assessments, refer to Section 10.7, Appendix 7, Clinical Laboratory Tests.

If the unscheduled ACTH test is performed further to the presence of signs and symptoms of adrenal insufficiency (as listed above), and the participant does not achieve a cortisol value %500 nmol/L (18.1 &g/dL) on at least 1 of the time points of cortisol measurement during the ACTH stimulation test (ie, morning basal cortisol or 60 minutes after ACTH stimulation), this should be discussed with the sponsor, taking into account other possible confounding factors (eg, concomitant medication, AEs,…), and the participant may discontinue ART and be withdrawn from the study if considered appropriate (refer to Section 7).

Appropriate clinical follow-up, including further endocrine evaluations, should be installed. The sponsor will seek external endocrinological advice should this be deemed appropriate or at request of the investigator. To this extent an external pediatric endocrinology expert will be available for the full duration of the study. In case of clinical signs or symptoms of adrenal insufficiency and an abnormal ACTH stimulation test it may be decided by the investigator and after consultation with the sponsor to discontinue ART if this is in the best interest of the participant. Other measures could be to start substitution therapy as appropriate. This may be the administration of glucocorticoids at the time of stressful events such as surgery or short or longer-term glucocorticoid substitution. In case of acute adrenal insufficiency participants may be hypovolemic, hyponatremic, or hyperkalemic. In such case initial therapy may consist of intravenously (IV) administered saline and dextrose. In a hypotensive participant, a 20 mL/kg bolus of isotonic sodium chloride solution given over the first hour may be necessary to restore the blood pressure. This bolus may be repeated if the blood pressure remains low. After results for the participant’s electrolytes, blood sugar, and cortisol are obtained, a single dose of dexamethasone may be administered without interfering with the cortisol response to cosyntropin or analogues, and an ACTH stimulation test should be performed. If adrenal insufficiency is diagnosed based on the results, substitution with glucocorticoids may need to be installed. The need for glucocorticoid replacement needs to be balanced between the need to prevent symptoms of adrenal insufficiency and the need to allow the participant to grow at a normal rate since excess replacement with glucocorticoid diminishes growth velocity. In case of reduced aldosterone secretion, mineralocorticoid replacement might also be required.

CLINICAL HEPATITIS

Nonviral Hepatitis

Participants should be monitored for the development of signs and symptoms of hepatitis, which include, but are not limited to, fatigue, malaise, anorexia, nausea, dark urine and clay-colored stools, bilirubinuria, jaundice, liver tenderness, with or without initially abnormal serum transaminase levels.

Participants with these signs and symptoms should seek medical attention immediately and hepatic parameters should be tested. Antiretroviral therapy must be permanently discontinued and the participant will be withdrawn from the study if the hepatitis is considered at least possibly related to RPV in the opinion of the investigator (refer to Section 7).

Viral Hepatitis

If acute viral hepatitis is diagnosed during the study, the participant should be permanently withdrawn from the study (refer to Section 7).

NEUROPSYCHOLOGICAL SYMPTOMS

Participants and/or their representatives should be informed that RPV may cause dizziness, insomnia, somnolence, and/or abnormal dreams (refer to Section 2.3.3) and instructed that if participants experience these symptoms they should avoid potentially hazardous tasks such as operating machinery.

There have been reports of delusions and inappropriate behavior in participants receiving licensed NNRTIs, especially in participants with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported. At all visits indicated in the Schedule of Activities (refer to Section 1.3) an evaluation will be done using questionnaires or other means (as available at the site) as part of local standard of care for this population, to assess whether the participant needs to be referred for a complete mental health assessment by a mental health professional (refer to Section 8.2.5). Participants who experience symptoms of depression and/or their representatives should contact the investigator immediately as discontinuation of ART may be required. Investigators should refer participants experiencing such symptoms for immediate psychiatric evaluation/medical intervention.

In case of grade 3 and grade 4 alterations in personality behavior or in mood, ART must be permanently discontinued and the participant will be withdrawn if the neuropsychological symptoms are considered at least possibly related to RPV in the opinion of the investigator (refer to Section 7).

GASTROINTESTINAL NAUSEA (WITH OR WITHOUT VOMITING)

Although common, nausea following initiation of ART usually subsides or resolves during the first few weeks of treatment.

Participants with ABC in their background regimen and developing gastrointestinal nausea should be evaluated for the possibility of ABC hypersensitivity reaction and follow the instructions related to clinically suspected hypersensitivity to ABC (refer to Hypersensitivity Reactions).

Grade 1 and **Grade 2 Nausea**

Participants may continue ART and may be treated as needed with anti-emetics given orally or by suppository.

Grade 3 Nausea

Participants will interrupt ART. The participant will be treated as needed with anti-emetics given orally or by suppository. Antiretroviral therapy may be resumed when the nausea resolves to grade ≤2.

If grade 3 nausea recurs after resuming ART despite the use of anti-emetics, participants will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

Grade 4 Nausea

Participants will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

DIARRHEA

Participants with ABC in their background regimen and developing diarrhea should be evaluated for the possibility of ABC hypersensitivity reaction and follow the instructions related to clinically suspected hypersensitivity to ABC (refer to Hypersensitivity Reactions).

Grade 1 and **Grade 2 Diarrhea**

Participants may continue ART. Loperamide or diphenoxylate can be administered.

Grade 3 Diarrhea

Participants will interrupt ART. Antiretroviral therapy may be resumed when the diarrhea resolves to grade ≤2.

If grade 3 diarrhea recurs after resuming ART despite the use of appropriate medication, participants will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

Grade 4 Diarrhea

Participants will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

OTHER TOXICITIES

Grade 1

Participants may continue ART.

Grade 2

Participants may continue ART based on the investigator's clinical judgment.

Grade 3

Participants should interrupt ART and may resume ART when the AE or laboratory abnormality resolved to within 1 grade level of the participant's baseline but not higher than grade 2.

The following exceptions apply:

- Participants with pre-existing diabetes who experience a glucose elevation of grade 3 (refer to Grade 3 or 4 Hyperglycemia).
- Participants who experience asymptomatic glucose, triglyceride, or cholesterol elevations of grade 3 (refer to Grade 3 or 4 Hyperglycemia and Grade 3 or 4 Hypertriglyceridemia and Grade 3 Hypercholesterolemia).
- Participants who experience asymptomatic pancreatic amylase elevations of grade 3 with no history or concomitant disease of pancreatitis.
- Participants who experience an AE that is considered not related or doubtfully related to RPV.

Grade 4

Participants will permanently discontinue ART and will be withdrawn from the study (refer to Section 7).

Exceptions are, unless clinical assessment foresees an immediate health risk to the participant:

- Participants with pre-existing diabetes who experience a glucose elevation of grade 4 (refer to Grade 3 or 4 Hyperglycemia).
- Participants who experience asymptomatic glucose or triglyceride elevations of grade 4 (refer to Grade 3 or 4 Hyperglycemia and Grade 3 or 4 Hypertriglyceridemia and Grade 3 Hypercholesterolemia).
- Participants who experience confirmed pancreatic amylase and lipase elevations of grade 4 (refer to PANCREATIC AMYLASE OR LIPASE ELEVATIONS).
- Participants who experience a grade 4 AE (except rash, allergic reaction, or neuropsychological event) that is considered not related or doubtfully related to RPV.

Note: This management scheme is for confirmed laboratory abnormalities and not for isolated events.

SPECIFIC TOXICITIES WITH CONCOMITANT ARVS

The information below does not imply that the following AEs are only related to concomitant ARVs, since a contribution of RPV cannot be excluded.

Grade 3 or 4 Hyperglycemia

Management decisions should be based on fasted results. If elevated glucose levels are from a nonfasting blood draw, the draw should be repeated after a 10-hour fast.

Participants who experience asymptomatic glucose elevations of grade 3 or 4 and participants with pre-existing diabetes may continue ART unless clinical assessment foresees an immediate health risk to the participant.

Participants without pre-existing diabetes and with persistent grade 3 or 4 glucose elevations (despite appropriate antidiabetic medication/management) should permanently discontinue ART and be withdrawn from the study (refer to Section 7). Appropriate clinical management of hyperglycemia must be started in a timely fashion.

Grade 3 or 4 Hypertriglyceridemia and Grade 3 Hypercholesterolemia

Management decisions should be based on fasted results. If elevated triglyceride or cholesterol levels are from a nonfasting blood draw, the draw should be repeated after a 10-hour fast.

Participants who experience asymptomatic triglyceride elevations of grade 3 or 4 or cholesterol elevations of grade 3 may continue ART.

Hypertriglyceridemia and hypercholesterolemia should be treated according to the specific guidelines for treating HIV-infected participants. Appropriate clinical management of cholesterol in the setting of HIV infection should be started in a timely fashion. Investigators may choose to initiate treatment with fenofibrate, gemfibrozil, clofibrate, niacin, or a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, in addition to the usual counseling on diet and exercise. These medications should be introduced with caution as they may have overlapping adverse effects. Moreover, niacin has the propensity to worsen the control of blood sugar in participants with diabetes mellitus or a history of hyperglycemia.

Hypersensitivity Reactions

In clinical studies, approximately 5% of participants receiving ABC developed a hypersensitivity reaction, which in rare cases has been proven fatal.[30]

At screening, all participants without prior documented HLA-B*5701-negative results in whom the investigator considers ABC in the background regimen will be tested for HLA-B*5701. In those participants where HLA-B*5701 is positive, ABC cannot be administered.[28]

Also in case of switch to ABC during the study, the participant should test negative for HLA-B*5701 (unless prior documented negative results are available).

It should also be noted that restricting ABC treatment to HLA-B*5701-negative participants (so excluding participants where HLA-B*5701 is positive) does not completely eliminate the risk of hypersensitivity reactions.

Description of the ABC Hypersensitivity Reaction

The ABC hypersensitivity reaction is characterized by symptoms indicating multi-organ involvement. The majority of participants have fever and/or rash.

Symptoms can occur at any time during ABC treatment, but usually appear within the first 6 weeks (median time to onset: 11 days). The symptoms worsen with continued therapy and can be life-threatening, and usually resolve shortly after discontinuation of ABC.

Frequently observed signs and symptoms include fever; rash; malaise or fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as dyspnea, sore throat, or cough. Other signs and symptoms include myalgia, arthralgia, oedema, pharyngitis, headache, paresthesia, and myolysis.

Physical findings may include rash (usually maculopapular or urticarial), lymphadenopathy, and mucous membrane lesions (conjunctivitis, mouth ulceration). Abnormal chest x-ray findings may also be present (predominantly infiltrates, which can be localized).

Laboratory abnormalities may include elevated liver function tests (such as hepatic transaminases), increased creatine phosphokinase or creatinine levels, and lymphopenia.

Anaphylaxis, hypotension, liver failure, renal failure, adult respiratory distress syndrome, and respiratory failure may occur as well.

Some participants with hypersensitivity were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis, or reactions to other medications. This delay in diagnosis leads to a more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for participants presenting with symptoms of these diseases. No ABC should be administered if a hypersensitivity reaction cannot be ruled out.

Management of ABC Hypersensitivity Reactions

Participants developing signs or symptoms possibly linked with a hypersensitivity reaction and/or their representatives must immediately contact the participant's doctor.

If a hypersensitivity reaction is diagnosed or if hypersensitivity cannot be ruled out (even when other diagnoses are possible [respiratory diseases, flu-like illness, gastroenteritis, or reactions to other medications]), the participant must immediately discontinue ABC treatment. The ABC-containing ARVs will be replaced by alternative ARVs. The participant and/or his or her representative should be asked to return all unused supplies of the ABC-containing ARVs for disposal to prevent an accidental rechallenge.

Symptomatic support for ABC hypersensitivity may be indicated such as the administration of IV fluids to participants who develop hypotension. Antihistamines or corticosteroids have been used to manage ABC hypersensitivity; however, there are no clinical data demonstrating their benefit in the management of the hypersensitivity reaction.

Laboratory and other investigations which may be useful in the evaluation and treatment of ABC hypersensitivity include, but are not limited to, measurement of ALT, AST, creatine phosphokinase, serum creatinine, and WBC differential count, and chest x-ray (if respiratory symptoms are present).

Special Considerations Following an Interruption of ABC Treatment

If ABC treatment has been interrupted and restarting is under consideration, the reason for interruption should be evaluated to ensure that the participant did not have symptoms of a hypersensitivity reaction. Restart of ABC treatment must be done only if access to appropriate medical care is readily available. If interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms, or a respiratory symptom), restarting of any ABC-containing ARV should be done only under direct medical supervision.

Essential Participant Information

Participants will be provided a warning card listing the common signs of a hypersensitivity reaction and will be instructed to carry this card with them at all times.

Investigators must ensure that participants and/or their representatives are fully informed regarding the following information on the hypersensitivity reaction:

- Participants and/or their representatives must be made aware of the possibility of a hypersensitivity reaction to ABC that may result in a life-threatening reaction or death.
- At screening, all participants without prior documented HLA-B*5701 negative results in whom the investigator considers ABC in the background regimen will be tested for HLA-B*5701. In those participants where HLA-B*5701 is positive, ABC cannot be administered.[28] In addition, in case of switch to ABC during the study, the participant should test negative for HLA-B*5701 (unless prior documented negative results are available).
- Participants developing signs or symptoms possibly linked with a hypersensitivity reaction and/or their representatives must immediately contact the participant's doctor.
- Participants who are hypersensitive to ABC and/or their representatives will be reminded that the participants must never take any ABC-containing ARV again.
- Participants who have experienced a hypersensitivity reaction will be asked to return all unused supplies of the ABC-containing ARVs for disposal to prevent an accidental rechallenge.

- Participants who have stopped taking an ABC-containing ARV for any reason (particularly due to possible adverse reactions or illness) and/or their representatives must be advised to contact the participant's doctor before restarting.

Reporting of Hypersensitivity Reaction

All cases of ABC hypersensitivity should be reported as SAEs (refer to Section 8.3).

Lactic Acidosis

The relevance of asymptomatic lactate elevations during ART is unclear. Therefore, routine lactate monitoring is not currently recommended and serum lactate evaluation is not part of the routine safety evaluations for this study. However, lactate monitoring should be performed at the local laboratory if there is a clinical suspicion of lactic acidosis (see description below).

Lactic acidosis syndrome, sometimes fatal and often associated with evidence of hepatic steatosis, is a recognized but rare complication of N(t)RTI therapy. Current knowledge regarding this syndrome is incomplete. Obesity and prolonged N(t)RTI exposure may be risk factors.

Lactic acidosis frequently involves nonspecific symptoms such as fatigue, weakness, and fever, but in the majority of cases also involves symptoms suggestive of hepatic dysfunction such as nausea, vomiting, abdominal or epigastric discomfort, abdominal distension, hepatomegaly, and new onset elevated liver enzymes.

A high index of suspicion may be required to diagnose this condition. Alternatively, it is possible that unwarranted concern may be raised by overinterpretation of lactic acid levels. N(t)RTI toxicity is only 1 cause of lactic acidosis. Type "B" lactic acid elevations or those without clinically apparent tissue hypoxia are also seen in the context of diabetes mellitus, uremia, liver disease, infections, malignancies, alkaloses, and drug and toxin ingestion of such substances as ethanol, methanol, ethylene glycol, and salicylates.

The following case definition of lactic acidosis will be used in this study:

Symptomatic Hyperlactatemia

New, otherwise unexplained, and persistent (%2 weeks) occurrence of at least 1 of the following symptoms:

- Nausea and vomiting
- Abdominal pain or gastric discomfort
- Abdominal distention
- Increased hepatic transaminases
- Unexplained fatigue
- Dyspnea
- Lactate level ≥2x ULN confirmed by repeat lactate level analysis

Note: All lactate levels ≥2x ULN should be repeated as soon as possible (local laboratory), generally within 1 week. If the second result confirms hyperlactatemia, participants should immediately interrupt their ART. Standard management should be initiated with follow-up to resolution. If causality is related to the background regimen only and NOT to RPV, N(t)RTIs must be changed. If causality is related to RPV, ART will be discontinued and participants will be withdrawn.

Processing of the lactate sample needs to be done according to strict guidelines both in the preparation of the participant (ideally, fasting and with no recent exercise) and in the blood drawing/processing procedure (ideally, blood drawn without a tourniquet, no hand clenching, and blood drawn into a chilled tube and processed immediately) to minimize false lactate elevations.

Renal Complications

Renal safety will be monitored by evaluating serum creatinine levels, estimated glomerular filtration rate (eGFR), serum chemistry, and urinalysis at the visits indicated in the General Schedule of Activities (refer to Section 1.3.1).

If eGFR is decreased with ≥30% from baseline, the value must be confirmed by repeat testing within 72 hours using an unscheduled visit. A sample for bioanalysis of RPV should be taken at the time of the unscheduled visit. If the decrease in eGFR is confirmed, ART interruption may be considered at the discretion of the investigator. If the abnormality is not confirmed, the participant may continue ART with close follow-up by the investigator.

Unscheduled visits may be used to monitor renal function more closely. Long-term follow-up of participants who develop nephrotoxicity should be discussed with the sponsor. Participants who change their background regimen or permanently discontinue ART due to nephrotoxicity must attend scheduled, unscheduled, or post-study follow-up visits to characterize resolution of renal abnormalities. Follow-up visits (scheduled, unscheduled, or post-study) will be conducted every 4 weeks and must be maintained until stabilization for 3 months with fluctuations of eGFR of <20% or return to baseline levels.

Pancreatitis

Pancreatitis must be considered whenever a participant receiving didanosine (ddI) (with or without concomitant administration of TDF) and/or stavudine (d4T) develops abdominal pain and nausea, vomiting, or elevated pancreatic amylase or lipase. Treatment with ddI, and/or TDF, and/or d4T should be interrupted until the diagnosis of pancreatitis is excluded. The participant experiencing pancreatitis can, however, be rechallenged with the ARV background regimen if pancreatitis is considered not related to this treatment.

In case the pancreatitis is considered at least possibly related to RPV, ART must be permanently discontinued and the participant will be withdrawn from the study (refer to Section 7).

Peripheral Neuropathy

Participants should be monitored for the development of peripheral neuropathy, which is usually characterized by numbness, tingling, and/or pain in the feet or hands. Peripheral neuropathy is a common AE of ddI and d4T.

Treatment of the peripheral neuropathy is at the discretion of the investigator, but generally begins with nonopioid analgesics, including nonsteroidal anti-inflammatory agents and acetaminophen (paracetamol), and the use of tricyclic antidepressants and other agents when more severe pain is present. Some of these medications should be introduced with caution.

10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

The investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local medical association (eg, American Academy of Pediatrics) or health department guidelines.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license).

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the participants).
- IB (or equivalent information) and amendments/addenda.
- Sponsor-approved participant recruiting materials.
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct).
- Revision(s) to ICF and any other written materials to be provided to participants.
- If applicable, new or revised participant recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- New edition(s) of the IB and its amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention.
- New information that may adversely affect the safety of the participants or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants.

- Report of deaths of participants under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data, or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS AND ASSENT FORM

Before any study-related activity, each participant’s representative must give written consent according to local requirements after the nature of the study has been fully explained. Sufficient time will be given to read the ICF and to ask questions. A copy of the ICF must be provided.

Assent must be obtained from children (minors) capable of understanding the nature of the study, typically participants aged ≥7 years, depending on the institutional policies. Children will be asked whether or not they wish to participate in the research, after having been informed about the study in a manner that is appropriate to their intellectual and emotional capacities. They will be informed to the fullest extent possible in language and terms they are able to understand. Written assent

should be obtained from participants who are able to write. A copy of the assent form must be provided.

The assent form and ICF must be approved by both the sponsor and by the reviewing IEC/IRB, and be in a language that the participant (if applicable) and his or her representative can read and understand. If the representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the representative is obtained. The informed consent process should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants and/or their representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail.

Participants and/or their representatives will be informed that participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that the records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the representative is authorizing such access. It also denotes that the participants and/or their representatives agree to allow the participants' study physician to recontact the participants and/or their representatives for the purpose of obtaining consent/assent for additional safety evaluations, if needed.

In case of rescreening, a new ICF and new assent form (if applicable) are to be obtained before rescreening.

The medical record must include a statement that consent and assent (if applicable and deemed appropriate by local ethics review) were obtained before the participant was enrolled in the study and must also include the date of written consent. The medical record should also describe how the investigator determined that the person signing the ICF was the participant's representative. The authorized person obtaining informed consent must also sign the ICF.

Participants and their representatives must be reconsented/re-assented to the most current version of the ICF/assent form (if applicable) during their participation in the study.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant's representative includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to the participant's original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participants and their representatives have the right to request through the investigator access to the participant's personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand RPV and to develop tests/assays related to RPV. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants and their representatives may withdraw their consent/assent for their samples to be stored for research (refer to Section 7.2, Participant Discontinuation/Withdrawal From the Study).

COMMITTEES STRUCTURE

Independent Data Monitoring

An IDMC will be established to monitor and review PK, safety, tolerability, and efficacy data (including individual growth and pubertal development as part of physical examination) on an ongoing basis and to ensure the continuing safety of the participants enrolled in this study. The IDMC will be the same committee as for the study C213 and will include at least 1 HIV specialist and at least 1 statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. After the review, the IDMC will make recommendations regarding the continuation of the study.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding RPV or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior

clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of RPV, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. If issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have

made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents into the CRF. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Details of physical examination
- Investigator-completed scales and assessments
- Diaries

The minimum source document requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical

study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF.

MONITORING

The sponsor will use a combination of monitoring techniques: remote and on-site monitoring.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such documents.

STUDY AND SITE CLOSURE

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Reasons for the early closure of a study site by the sponsor may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

10.4 Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and in Section 10.8, Appendix 8 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Girl of Childbearing Potential

A girl is considered fertile following menarche.

Girl not of Childbearing Potential

A girl in premenarchal state; in whom menarche has not yet occurred.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal girl experiences menarche) or the risk of pregnancy changes (eg, a girl who is not heterosexually active becomes active), a girl must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

USER INDEPENDENT

Highly effective methods that are user independent - failure rate of ≤1% per year when used consistently and correctly.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the girl of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)

USER DEPENDENT

Highly effective methods that are user dependent - failure rate of ≤1% per year when used consistently and correctly.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
- Sexual abstinence
  (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom [b]
- Cap, diaphragm, or sponge
- A combination of male condom with either cap, diaphragm, or sponge (double barrier methods)[b]
- Periodic abstinence (calendar, symptothermal, postovulation methods)
- Withdrawal (coitus-interruptus)
- Lactational amenorrhea method

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy during the study

Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

For a female participant who becomes pregnant, this information will be shared with the participant's representative.

10.5 Appendix 5: DAIDS Table

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

The DAIDS grading table is a descriptive terminology to be utilized for AE reporting in this study. A grading (severity) scale is provided for each AE term.

General Instructions

Grading Adult and Pediatric Adverse Events

When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If there is no distinction between adult and pediatric populations, the listed parameter should be used for grading an AE in both populations.

Determining Severity Grade for Parameters Between Grades

If the severity of an AE could fall under either 1 of 2 grades (eg, the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the 2 grades.

Laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

Basic self-care functions	Adults: activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding Young children: activities that are age and culturally appropriate (eg, feeding self with culturally appropriate eating implements)
Usual social & functional activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults: adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby Young Children: activities that are age and culturally appropriate (eg, social interactions, play activities, learning tasks)
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an AE.

Estimating Severity Grade for Parameters not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical AE **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[a] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *aged ≥18 years*	140 to <160 mmHg systolic OR 90 to <100 mmHg diastolic	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
aged <18 years	>120/80 mmHg	≥95th to <99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only 1*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

NA=not applicable

a Blood pressure norms for children aged <18 years can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children, packed RBCs >10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only 1* *aged >16 years*	PR interval 0.21 to <0.25 seconds	PR interval ≥0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
aged ≤16 years	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block
Prolonged QTc Interval[b]	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥0.06 seconds above baseline	Life-threatening consequences (eg, TdP, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only 1*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (eg, pulmonary embolism, thrombus)

AV=atrioventricular, NA=not applicable
b As per Bazett's formula.

DERMATOLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to 1 area	Localized to more than 1 area	Generalized	NA
Cellulitis	NA	Nonparenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to 1 area	Localized to more than 1 area	Generalized	NA
Pruritus[c] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to 1 site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

NA=not applicable

c For pruritus associated with injections or infusions, refer to the SITE REACTIONS TO INJECTIONS AND INFUSIONS section.

ENDOCRINE AND METABOLIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (eg, ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy[d]	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[e]	Detectable by participant, representative, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

NA=not applicable
d A disorder characterized by fat loss in the face, extremities, and buttocks.
e A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only 1*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea *aged ≥1 year*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
aged <1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (eg, liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only 1 and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (eg, hypotensive shock)

NA=not applicable

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Mucositis or Stomatitis *Report only 1 and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

NA=not applicable

MUSCULOSKELETAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[f] *aged ≥30 years*	BMD t-score -2.5 to -1	NA	NA	NA
aged <30 years	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[f] *aged ≥30 years*	NA	BMD t-score <-2.5	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
aged <30 years	NA	BMD z-score <-2	Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

BMD=bone mineral density, NA=not applicable

f Bone mineral density t- and z-scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (eg, stroke with neurological deficit)
Altered Mental Status (for Dementia, refer to *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *Specify type, if applicable aged <18 years*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

NA=not applicable

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *aged ≥18 years*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
aged <18 years (includes new or pre-existing febrile seizures)	Seizure lasting <5 minutes with <24 hours postictal state	Seizure lasting 5 to <20 minutes with <24 hours postictal state	Seizure lasting ≥20 minutes OR >24 hours postictal state	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (eg, severity or focality)	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Syncope	Near syncope without loss of consciousness (eg, pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

NA=not applicable

PREGNANCY, PUERPERIUM, AND PERINATAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Stillbirth (report using mother's participant ID) *Report only 1*	NA	NA	Fetal death occurring at ≥20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to <37 weeks gestational age	Live birth at 28 to <34 weeks gestational age	Live birth at 24 to <28 weeks gestational age	Live birth at <24 weeks gestational age
Spontaneous Abortion or Miscarriage[g] (report using mother's participant ID) *Report only 1*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

ID=identity, NA=not applicable
g A pregnancy loss occurring at <20 weeks gestational age.

PSYCHIATRIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only 1*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

NA=not applicable

RESPIRATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70% to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50% to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25% to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only 1*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to <95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (eg, CPAP, BPAP, intubation)

BPAP=biphasic positive airway pressure, CPAP=continuous positive airway pressure, NA=not applicable

SENSORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hearing Loss *aged ≥12 years*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Nonserviceable hearing (ie, >50 dB audiogram and <50% speech discrimination)
aged <12 years (based on a 1, 2, 3, 4, 6, and 8 kHz audiogram)	>20 dB hearing loss at ≤4 kHz	>20 dB hearing loss at >4 kHz	>20 dB hearing loss at ≥3 kHz in 1 ear with additional speech-language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

dB=decibel, kHz=kilohertz, NA=not applicable

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[h]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only 1*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0°C to <38.6°C or 100.4°F to <101.5°F	≥38.6°C to <39.3°C or ≥101.5°F to <102.7°F	≥39.3°C to <40.0°C or ≥102.7°F to <104.0°F	≥40.0°C or ≥104.0°F
Pain[i] (not associated with study intervention injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[j]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)

NA=not applicable

h A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

i For pain associated with injections or infusions, refer to the SITE REACTIONS TO INJECTIONS AND INFUSIONS section.

j A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Underweight[k] *aged >5 to 19 years*	WHO BMI z-score <-1 to -2	WHO BMI z-score <-2 to -3	WHO BMI z-score <-3	WHO BMI z-score <-3 with life-threatening consequences
aged 2 to 5 years	WHO Weight-for-height z-score <-1 to -2	WHO Weight-for-height z-score <-2 to -3	WHO Weight-for-height z-score <-3	WHO Weight-for-height z-score <-3 with life-threatening consequences
aged <2 years	WHO Weight-for-length z-score <-1 to -2	WHO Weight-for-length z-score <-2 to -3	WHO Weight-for-length z-score <-3	WHO Weight-for-length z-score <-3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5% to <9% loss in body weight from baseline	≥9% to <20% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

NA=not applicable

k WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants aged >5 to 19 years and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those aged ≤5 years.

URINARY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

NA=not applicable

SITE REACTIONS TO INJECTIONS AND INFUSIONS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pain or Tenderness *Report only 1*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[1] *Report only 1* *aged >15 years*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
aged ≤15 years	≤2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (eg, upper arm or thigh)	≥50% surface area of the extremity segment involved (eg, upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only 1* *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*	Same as for **Injection Site Erythema or Redness**, *aged >15 years*
aged ≤15 years	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*	Same as for **Injection Site Erythema or Redness**, *aged ≤15 years*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

NA=not applicable

1 Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

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	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]	Refer to Appendix A[o]

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.

o Appendix A "Total Bilirubin Table for Term and Preterm Neonates" is provided together with the DAIDS table corrected version 2.1 at the following URL: https://rsc niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Appendix A is not applicable for this study.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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*[p]	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[q] **or eGFR, Low** *Report only 1*[p]	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

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

q Use the applicable formula (ie, Cockcroft-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[r], 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

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

LABORATORY VALUES				
HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute CD4+ Count, Low (cells/mm³; *cells/L*) *aged >5 years (not HIV-infected)*	300 to <400 *0.300×10⁹ to <0.400×10⁹*[s]	200 to <300 *0.200×10⁹ to <0.300×10⁹*[s]	100 to <200 *0.100×10⁹ to <0.200×10⁹*[s]	<100 *<0.100×10⁹*[s]
Absolute Lymphocyte Count, Low (cells/mm³; *cells/L*) *aged >5 years (not HIV-infected)*	600 to <650 *0.600×10⁹ to <0.650×10⁹*	500 to <600 *0.500×10⁹ to <0.600×10⁹*	350 to <500 *0.350×10⁹ to <0.500×10⁹*	<350 *<0.350×10⁹*
Absolute Neutrophil Count, Low (cells/mm³; *cells/L*) *aged >7 days*	800 to 1,000 *0.800×10⁹ to 1.000×10⁹*	600 to 799 *0.600×10⁹ to 0.799×10⁹*	400 to 599 *0.400×10⁹ to 0.599×10⁹*	<400 *<0.400×10⁹*
aged 2 to 7 days	1,250 to 1,500 *1.250×10⁹ to 1.500×10⁹*	1,000 to 1,249 *1.000×10⁹ to 1.249×10⁹*	750 to 999 *0.750×10⁹ to 0.999×10⁹*	<750 *<0.750×10⁹*
aged ≤1 day	4,000 to 5,000 *4.000×10⁹ to 5.000×10⁹*	3,000 to 3,999 *3.000×10⁹ to 3.999×10⁹*	1,500 to 2,999 *1.500×10⁹ to 2.999×10⁹*	<1,500 *<1.500×10⁹*
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[t], Low (g/dL; *mmol/L*)[u] *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

s Revised by the sponsor.

t 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).

u 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

NA=not applicable

10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV

Drug Class	Interaction Effect	Clinical Comment
● Medication with risk for TdP		
- Bepridil	Data on interaction with RPV currently not available.	**Disallowed.**
- Cisapride	Data on interaction with RPV currently not available.	**Disallowed.**
- Pimozide	Data on interaction with RPV currently not available.	**Disallowed.**
- Arsenic trioxide	Data on interaction with RPV currently not available.	**Use with caution.** Additional safety monitoring is required if taken for >2 days[a].
- Chloroquine, halofantrine	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].
- Chlorpromazine, haloperidol, mesoridazine, thioridazine, droperidol	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].
- Clarithromycin, erythromycin, telithromycin, troleandomycin, roxithromycin Note: azithromycin is preferred option	Data on interaction with RPV currently not available.	**Use with caution**. Plasma concentrations of RPV may be increased when coadministered. Additional safety monitoring is required if taken for >2 days[a]. Azithromycin is expected to have no or minimal effect on RPV plasma concentrations and is therefore the preferred option for treatment with macrolide antibiotics; no additional monitoring is required for azithromycin coadministration.
- Dofetilide, ibutilide, procainamide, sotalol	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a]
- Domperidone	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].
- Flecainide, propafenone, systemic lidocaine, mexilitine	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].
- Levomethadyl	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].
- Methadone	RPV reduces the exposures (AUCs) of R-methadone and S-methadone by 16%.	**Use with caution**. Plasma concentrations of methadone may be decreased when coadministered with RPV. No dose adjustments are required. Monitor for signs and symptoms of methadone withdrawal; some participants may need an increase in the methadone dose. Additional safety monitoring is required if taken for >2 days[a].
- Probucol	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].

Drug Class	Interaction Effect	Clinical Comment
- Quinidine, disopyramide, amiodarone	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].
- Sparfloxacin, pentamidine	Data on interaction with RPV currently not available.	**Use with caution**. Additional safety monitoring is required if taken for >2 days[a].
● Anticonvulsants		
- Phenobarbital, carbamazepine, oxcarbazepine, and phenytoin	Data on interaction with RPV currently not available.	**Disallowed**. Coadministration may result in reduced RPV plasma concentrations and in loss of therapeutic effect.
- Modafinil	Data on interaction with RPV currently not available.	**Disallowed**. Coadministration may result in reduced RPV plasma concentrations and in loss of therapeutic effect.
● Antidiabetic agents		
- Pioglitazone, troglitazone	Data on interaction with RPV currently not available.	**Disallowed**. Coadministration may result in reduced RPV plasma concentrations and in loss of therapeutic effect.
● Calcium channel blockers		
- Verapamil, diltiazem	Data on interaction with RPV currently not available.	**Use with caution.** Plasma concentrations of RPV may be increased when coadministered. Additional safety monitoring is required if taken for >2 days[a].
● Azole antifungal agents		
- Ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole Note: fluconazole is preferred option	Ketoconazole increased the exposure to RPV by 50% for AUC and by 30% for C_{max}.	**Use with caution.** Plasma concentrations of RPV may be increased by coadministration of these medications. Additional safety monitoring is required if taken for >2 days[a]. Fluconazole in a dose of 200 mg/day is expected to have no or minimal effect on RPV plasma concentrations and is therefore the preferred option for treatment with azole antifungal agents; additional safety monitoring is only required for fluconazole coadministration when used in doses of 400-800 mg/day.
● Antibiotics		
- Rifabutin, rifampicin, rifapentine	Rifabutin reduced exposure (AUC) to RPV by 42%. Rifampicin reduced exposure (AUC) to RPV by 80%. No data available on interaction with rifapentine.	**Disallowed**. Coadministration may result in reduced RPV plasma concentrations and in loss of therapeutic effect.

Drug Class	Interaction Effect	Clinical Comment
● Glucocorticoids		
- Dexamethasone (systemic and more than a single dose)	Data on interaction with RPV currently not available.	**Disallowed** (only topical and inhalation products allowed*). Coadministration may result in reduced RPV plasma concentrations and in loss of therapeutic effect. Could suppress adrenal gland function. *use of both chronic inhaled and intranasal dexamethasone is disallowed within 30 days before baseline and within 30 days before ACTH stimulation testing (only for participants aged ≥6 to <12 years, including participants who turn 12 years old during the study). Occasional use of either inhaled or intranasal steroids is allowed.
- Other glucocorticoids	Data on interaction with RPV currently not available.	**Disallowed if chronic** (topical and inhalation products allowed*). Could suppress adrenal gland function. *use of both chronic inhaled and intranasal steroids is disallowed within 30 days before baseline and within 30 days before ACTH stimulation testing (only for participants aged ≥6 to <12 years, including participants who turn 12 years old during the study). Occasional use of either inhaled or intranasal steroids is allowed.
● Progestogens		
- Megestrol acetate	Data on interaction with RPV currently not available.	**Disallowed**. Could suppress adrenal gland function.
● Proton pump inhibitors		
- eg, omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole	Omeprazole reduced the steady-state exposure (AUC) of RPV by 40%.	**Disallowed.** Coadministration of proton pump inhibitors reduces the plasma concentrations of RPV, and may result in loss of therapeutic effect.
● H_2-receptor antagonists and antacids		
- H_2-blockers (cimetidine, ranitidine, famotidine, nizatidine)	Famotidine taken 2 hours before RPV reduced the exposure (AUC) by 76%. There was no interaction after separate intake.	**Use with caution.** H_2-blockers should be taken at least 12 hours before or 4 hours after RPV intake.
- Antacids (eg, aluminium/magnesium hydroxide, calcium carbonate)	Data on interaction with RPV currently not available.	**Use with caution.** Antacids should be taken at least 2 hours before or 4 hours after RPV intake.
● St John's wort	Data on interaction with RPV currently not available.	**Disallowed.** Coadministration may result in reduced RPV plasma concentrations and in loss of therapeutic effect.

● Antiemetics		
- Aprepitant	Data on interaction with RPV currently not available.	**Use with caution.** Coadministration may result in increased plasma concentrations of RPV. Additional safety monitoring is required if taken for >2 days[a].

Drug Class	Interaction Effect	Clinical Comment
● Antidepressants		
- Nefazodone	Data on interaction with RPV currently not available.	**Use with caution.** Coadministration may result in increased plasma concentrations of RPV. Additional safety monitoring is required if taken for >2 days[a].

[a] The required additional safety monitoring consists of an unscheduled ECG taken 3 to 7 days after initiation of the comedication, taken at approximately 4 hours after RPV intake. Also, a PK sample needs to be drawn within 10 minutes after the ECG. The date and time of sampling and last RPV intake prior to PK sampling should be recorded on the CRF. If the participants experience a QTcF %480 ms that is confirmed by another ECG (repeat ECG should be performed within 48 hours after the site has received the abnormal result), the comedication should be stopped, if possible. Approximately 1 week after the comedication was stopped an ECG should be taken again to ensure normalization. If comedication treatment cannot be stopped, the participant should be withdrawn from the study. Approximately 1 week after withdrawal, another ECG should be performed during an unscheduled visit to ensure normalization.

Note: The list of disallowed concomitant medication and medication to be used with caution is not exhaustive; for products falling in one of the categories and not mentioned by name, the Sponsor should be contacted to determine whether the product can be allowed.

10.7 Appendix 7: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory (unless indicated otherwise):

Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCH concentration	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Chloride Calcium Calcium corrected for albumin Magnesium Phosphate Bicarbonate Blood urea nitrogen Uric acid Creatinine Human serum albumin Total protein AST/Serum glutamic-oxaloacetic ALT/Serum glutamic-oxaloacetic GGT	Alkaline phosphatase Total, direct, and indirect bilirubin Pancreatic amylase Lipase Glucose (fasting) Insulin Cholesterol HDL cholesterol LDL cholesterol Triglycerides	
	Note: Lactate will be assessed in case of suspicion of lactic acidosis syndrome (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities) and creatine phosphokinase will be assessed in case of suspicion of rhabdomyolysis. These assessments will be done at the local laboratory. The central laboratory will calculate the eGFR according to the following formula[32]: $eGFR = \frac{k * L\ (cm)}{\text{Plasma creatinine } (P_{cr})\ (mg/dL)}$ k = 0.55 in children aged 2-12 years, 0.55 in adolescent girls aged 13-21 years, and 0.70 in adolescent boys aged 13-21 years.		

Endocrine Tests (only for participants aged ≥6 to <12 years, including participants who turn 12 years old during the study)	FSH, LH, androstenedione, testosterone, 17-hydroxyprogesterone and DHEAS, in conjunction with cortisol. **At the time of protocol Amendment 2 writing,** 240-week results from C213 Cohort 1 (adolescents aged ≥12 to <18 years) are available. The 4-year follow-up data in adolescents did not show an effect on pubertal development. No clinically relevant suppression of cortisol secretion is observed in adults[27,29] or adolescents aged ≥12 to <18 years (C213 Cohort 1).[34,35] Also, in the first 9 children aged ≥6 to <12 years in C213 Cohort 2 there were no emergent cortisol abnormalities and no signs or symptoms of adrenal insufficiency.[24] Therefore an ACTH stimulation test, including measurements of cortisol and 17-hydroxyprogesterone, will be performed for all participants in the morning between 7h30 and 9h30 in case of confirmed abnormally low cortisol (<248 nmol/L [9 µg/dL] or signs or symptoms of adrenal insufficiency. After a sample for the determination of these endocrine parameters has been drawn (T_0), 250 µg of tetracosactide or cosyntropin will be injected IV over 2 minutes or intramuscularly and an additional blood sample will be collected 60 minutes (T_{60}) after injection for the determination of cortisol and 17-hydroxyprogesterone. If the ACTH stimulation test results are abnormal (ie, the cortisol value after ACTH stimulation is <500 nmol/L [18.1 µg/dL]), a retest needs to be performed at the next scheduled visit or at least within the next 8 weeks, including during the follow-up period. If the repeat ACTH stimulation test results are normal, the participant should continue study treatment. If the test results are abnormal, but the participant is asymptomatic, the sponsor should be notified. If the test results are abnormal, and the participant has symptoms consistent with adrenal insufficiency (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities), withdrawal of the participant should be discussed with the sponsor. In case of clinical signs or symptoms or laboratory abnormalities (other than cortisol) indicative of adrenal insufficiency (refer to Section 10.2, Appendix 2, Monitoring and Safety for Specific Toxicities), an ACTH stimulation test should be done as soon as possible during an unscheduled visit. If the ACTH stimulation test is abnormal (ie, the cortisol value after ACTH stimulation is <500 nmol/L [18.1 µg/dL]), withdrawal of the participant should be discussed with the sponsor.
Routine Urinalysis	Dipstick: Glucose, Protein, Blood Sediment (if dipstick result is abnormal): RBCs, WBCs, Casts If dipstick result is abnormal, microscopy will be used to measure sediment. In the microscopic examination, observations other than the presence of WBC, RBC, and casts may also be reported by the laboratory.
Other Screening Tests	Serum pregnancy testing at screening for girls of childbearing potential only. Serology (hepatitis A antibody, hepatitis B surface antigen, and hepatitis C virus antibody) at baseline.
Additional Tests	In addition to the serum pregnancy test at screening (see above), a urine pregnancy test will be performed at the other time points indicated in the Schedule of Activities for girls of childbearing potential only. Additional tests may be performed at the central laboratory, if needed. However, additional testing requires approval from the sponsor.

HDL=high-density lipoprotein, LDL=low-density lipoprotein, MCH=mean corpuscular hemoglobin, MCV=mean corpuscular volume

10.8 Appendix 8: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition per ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For RPV, the expectedness of an AE will be determined by whether or not it is listed in the IB. For ARVs allowed per protocol with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the study intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An AE that is not related to the use of the study intervention.

Doubtful

An AE for which an alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is more likely or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the study intervention. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the study intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is less likely.

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade will be made using the general categorical descriptors outlined in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (refer to Section 10.5, Appendix 5, DAIDS Table).

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on RPV that may require expedited reporting or safety evaluation include, but are not limited to:

- RPV overdose
- Suspected abuse/misuse of RPV
- Accidental or occupational exposure to RPV
- Unexpected therapeutic or clinical benefit from use of RPV
- Medication error involving RPV (with or without participant exposure to RPV, eg, name confusion)
- Exposure to RPV from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source documents and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source documents and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number

For participants who do not roll over in the pediatric study TMC278IFD3004, all AEs still ongoing at the end of the treatment will be followed until satisfactory resolution (ie, value back to baseline value) or stabilization (to be agreed upon in collaboration with the sponsor).

New AEs reported during the follow-up period of the study will be followed as agreed between the sponsor and investigator. Certain long-term AEs of ART cannot be followed until resolution within the setting of this protocol; in these cases, follow-up will be the responsibility of the treating investigator. However, this has to be agreed upon with the sponsor.

Serious Adverse Events

The start date of the SAE documented on the SAE form should be the date the AE first fulfilled any serious criterion. If a change in severity is noted for the existing AE, it must be recorded as a new AE. If a worsened AE meets the criteria for an SAE, the start date of the SAE must be the same as the start date of the worsened AE.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study, whether or not the event is expected or associated with the study intervention, is considered an SAE.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

After termination of the clinical study (last participant last visit in the study), any unexpected safety issue that changes the benefit/risk analysis and is likely to have an impact on the participants who have participated in it, should be reported as soon as possible to the competent authority(ies) concerned together with proposed actions.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

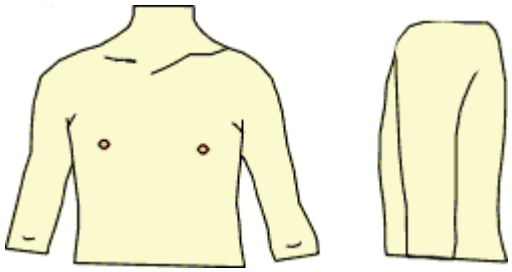
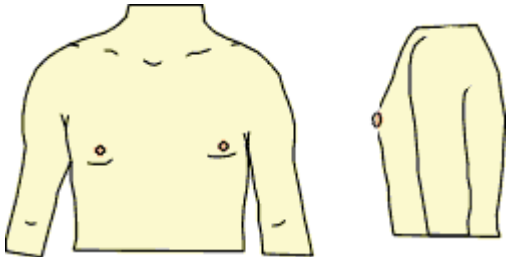
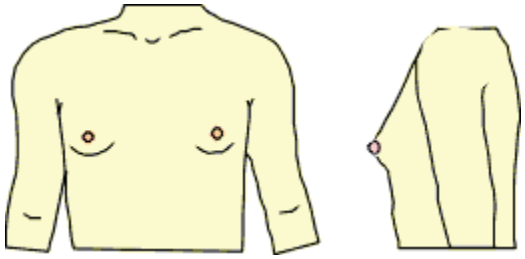
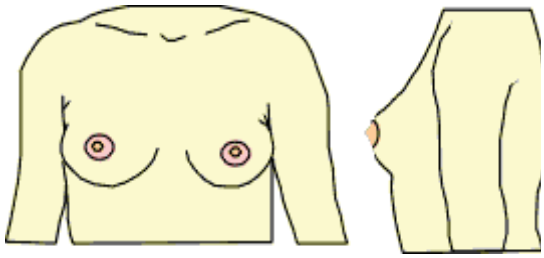
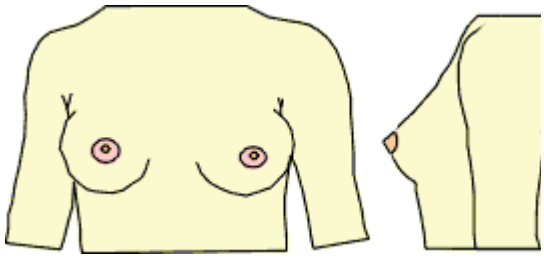
Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.9 Appendix 9: Tanner Scales

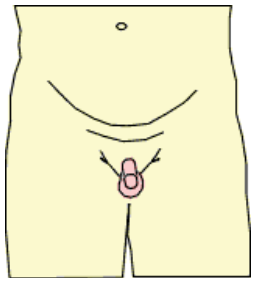
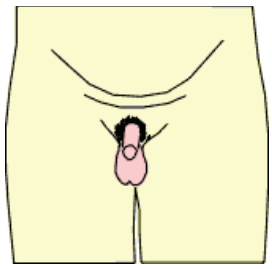
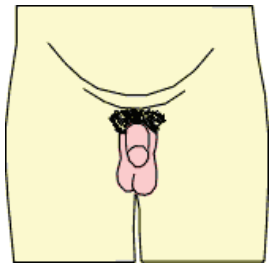
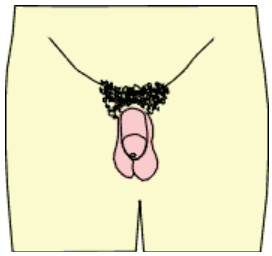
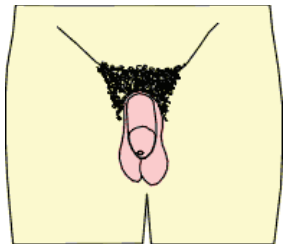
The Five Stages of Female Breast and Pubic Hair Development

Breast and pubic hair development should be staged separately

Stage		Female breast	Pubic hair
1		Breasts during childhood. The breasts are flat and show no signs of development.	None
2		Breast bud stage. Milk ducts and fat tissue forms a small mound.	Sparse, lightly pigmented, straight, medial border of labia.
3		Breasts continue to grow. Breasts become rounder and fuller.	Darker, beginning to curl, increased amount.
4		Nipple and areola form separate small mound. Not all girls go through this stage. Some skip stage 4 and go directly to stage 5.	Coarse, curly, abundant, but amount less than in adult.
5		Breast growth enters final stage. Adult breast is full and round shaped.	Adult feminine triangle, spread to medial surface of thighs.

The Five Stages of Male Genitalia and Pubic Hair Development

Genitalia and Pubic hair should be staged separately

Stage		Male Genitalie	Pubic hair
1		Penis and testicles of a child. Testicles between 1 and 3 milliliters in volume.	No pubic hair.
2		First signs of penis and testicle growth. Testicles become larger. Testicles between 4 and 6 milliliters in volume.	Pubic hair beginning to grow: appears sparse and downy straight.
3		Penis continues to grow getting wider and longer. Testicles continue to grow larger. Testicles between 7 and 16 milliliters in volume.	Pubic hair appears curlier and coarser with increased pigmentation.
4		Penis continues to grow getting wider and longer. Testicles continue to grow larger. Penis gland or head is more developed. Testicles between 12 and 24 milliliters in volume. Testicles are about 1 ½ inches long.	Pubic hair becomes adult type, but less.
5		Penis growth enters final stage. Average erect penis length 6 ¼ inches. 90% are 5 to 7 inches. Glans penis or head is fully developed. Testicles 16-27 milliliters in volume. Testicles are about 1 to 3/4 inches.	Pubic hair is thick, spreading to medial thighs.

10.10 Appendix 10: Pediatric European Network for the Treatment of AIDS (PENTA) Adherence Questionnaire

Note: This appendix provides a representative example of the questions that will be used in this study. The site should always use the most recently provided version of the questionnaire.

STUDY ADHERENCE QUESTIONNAIRE FOR CAREGIVERS

To the investigator/trial personnel: please complete the following table and write the names, color and type of medicines that the child has been taking in the tables in question 2 and 8.

Completed by Parent/carer alone? *Yes* *No* If **no**, who else was involved? _____	If not completed: Not enough time Refusal Parent/carer not available Other *specify:* _____

To the carer:

We know that it can be difficult giving antiretroviral medicines to children every day. We are interested in finding out what it is like for you and your family. Please tick the answer which best describes your true situation or feeling, as your answers may help others in the future. Thank you.

1) Do you give antiretroviral medicines to your child? _____

2) At what time do you usually give your child their antiretroviral medicines?

Name of medicine	Colour, Type	Timing of dosing	a.m./ p.m.
1. RPV			
2.			
3.			

3) Which dose, if any, is the most difficult for you or your child?

None morning lunchtime/after school evening all

4) How easily do you remember to give all the medicines to your child?

Easily quite easily with some difficulty with great difficulty

5) What helps you give the medicines? (tick all that apply)

Labels Medicine Chart Pill box MEM Caps Timer/alarm clock/beeper

Diary Daily events (e.g., breakfast time)

Other *Name them:*_____

6) How much does giving medicines to your child interfere with you/your child's everyday life?

A lot quite a lot not much not at all

How? _____

7) How important do you think it is to administer the medicines in the way indicated by the doctor (e.g. remembering to take every dose?)

Extremely Very Don't know Not very Not at all

8) Over the last 3 days, can you say how many times, your child has missed a dose:

No medicine missed

Drug	Yesterday	Day before yesterday	3 days ago
1. RPV	….. dose(s) missed	….. dose(s) missed	….. dose(s) missed
2.			
3.			

9) Since the last visit, when was the last time you missed a dose of any medication?

Never
During the previous 2 weeks
During the last month
Over a month ago
Don't remember

10) If your child has missed any doses during the last two weeks, please indicate the reason(s) and say which medicine(s) :

No medicine missed

Because:		Name of medicine
You had run out of medicine?		
Your child has problems taking some of the medicine?		
You had forgotten?		
You think the medicines are toxic or harmful?		
Taking the medicine is difficult with school hours, meals, sleep etc		
Your child refused to take them		
Your child was being looked after by someone else?		
You did not want other people to know your child was taking medicine?		
Your child was unwell?		
Your routine, or your child's routine, was different from normal (e.g., holidays, weekends etc)?		

Further details or any other reason (please specify): _____

_____

Thank you for taking the time to fill out this form, please add any comments you have:

_____

_____

STUDY ADHERENCE QUESTIONNAIRE FOR CHILDREN

Note: This questionnaire is a sample questionnaire. The site should always use the most recently provided version of the questionnaire.

Study Adherence Questionnaire for Children

To the investigator/study-site personnel: please complete the following table and write the names, color and type of the medicines that the child has been taking in the tables in question 1 and 8.

To be completed by the investigator/trial personnel:

Completed by patient alone?	If not completed:
Yes *No* If **no**, who else was involved? _____	Not enough time Refusal Other *specify:* _____

To be completed by the patient (for children 6 years of age and older)

We know that it can be difficult taking medicines every day. We are interested in finding out what it is like for you and your family. Please tick the answer which best describes your true situation or feeling, as your answers may help others in the future. Thank you.

1) At what time do you usually take your medicines?

Name of medicine	Color, Type	Time of dosing	a.m./p.m.
1. RPV			
2.			
3.			

2) Which dose, if any, is the most difficult?

None morning lunchtime/after school evening all

3) Does anyone remind you when to take your medicine? Yes No

If someone reminds you, who is it? _____

4) How easily do you remember to take all your medicines?

Easily quite easily with some difficulty with great difficulty

5) What helps you take the medicine? (Tick all that apply)

Labels Medicine chart Pill box MEM Caps

Alarm clock/Timer/beeper Diary Daily events (e.g., breakfast time)

Text messages Support from Mum/Dad/Carer Knowing my blood results

Knowing why I need to take medicines

Other *Namely*:_____

6) How much does taking medicines interfere with your life?

A lot quite a lot not much not at all

How? _____

7) How important do you think it is to take the medicines in the way your doctor told you (e.g. remembering to take every dose?)

Extremely Very Don't know Not very Not at all

8) Over the last 3 days, can you say how many times, you have missed a dose:

No doses missed

Drug	Yesterday	Day before yesterday	3 days ago
1. RPV	….. dose(s) missed	….. dose(s) missed	….. dose(s) missed
2.			
3.			

9) Since the last visit, when was the last time you missed a dose of any medication?

Never
During the previous 2 weeks
During the last month
Over a month ago
Don't remember

10) If you have missed any doses during the last two weeks, please tick the reason(s) why and say which medicine:

No doses missed

Because :		Name of medicine
You had run out of medicine ?		
You had forgotten?		
You think the medicine is toxic or harmful?		
Taking medicine is difficult with school hours, meals, sleep etc		
You didn't want to take it?		
You did not want other people to know you were taking medicine?		
You were unwell?		
Your routine was different from normal (e.g., holidays, weekends etc)?		
You are fed up taking medicine?		

Further details or any other reason (please specify): _____

_____

Thank you for taking the time to fill out this form, please add any comments you have:

10.11 Appendix 11: Palatability Questionnaire

Note: This appendix provides a representative example of the questions that will be used in this study. The site should always use the most recently provided version of the questionnaire.

PALATABILITY QUESTIONNAIRE FOR CHILDREN

CHILDREN'S RILPIVIRINE TASTE TEST

Today we are asking children like you about how you like the taste of the study medication rilpivirine when mixed in water

You do not have to take this test if you wish so.

ASK CHILD:

1. **How does this study medication taste to you, when you drink it after mixing it with water?**

   (Please look at the pictures and check ✓ ONLY one box for your answer).

READ SCALE AND POINT TO THE PICTURES

(If the child cannot convey their taste perception, parents can help the child)

				
Really Good	**Pretty Good**	**Okay**	**Not good**	**Terrible**
☐	☐	☐	☐	☐

Comments: _____

_____

Thank you for participating in this taste evaluation process; you have been very helpful.

10.12 Appendix 12: Swallowability Questionnaire

Note: This appendix provides a representative example of the questions that will be used in this study. The site should always use the most recently provided version of the questionnaire.

QUESTIONS FOR THE CHILD:

Please answer the questions below. There is no right or wrong answer. We just want to know how you have been feeling about swallowing the study pill.

1. Please tell us how easy or hard it was to swallow the tablet?
   (Please check ✓ ONLY one box for your answer)

hard	neither hard nor easy	easy
		
☐	☐	☐

2. If you would have to take the tablet once daily for a longer period, how would you describe it?
   (Please check ✓ ONLY one box for your answer)

Not acceptable	Acceptable	Good to take
		
☐	☐	☐

Comments: _____

_____

_____

Thank you for taking the time to fill out this form.

To the investigator/trial personnel: please answer the questions below.

QUESTIONS FOR THE OBSERVER:

1. Indicate how the tablet was taken

☐ swallowed with water

☐ mixed with tablespoon of semi-solid food and drinking water afterwards

2a. Did the patient have problems swallowing the tablet?

☐ No ☐ Yes

If no, go to Question 3
If yes, continue here:

Indicate which problems

☐ Refusing (could not take it)

☐ Vomiting/spitting up

☐ Gagging

☐ Other, specify _____

2b. Did the patient need a second attempt?

☐ No ☐ Yes

If no, go to Question 3
If yes, continue here

Did the patient have problems swallowing the tablet at the second attempt?

☐ No ☐ Yes

If no, go to Question 3
If yes, continue here

Indicate which problems

☐ Refusing (could not take it)

☐ Vomiting/spitting up

☐ Gagging

☐ Other, specify _____

3. Are there any other comments related to the intake of the tablet?

☐ No ☐ Yes

If no, STOP

If yes, please specify the comments

_____

_____

_____

10.13 Appendix 13: Cardiovascular Safety - Abnormalities

ECG

QTc interval[a]:

- Grade 1: ≥450 to ≤470 ms
- Grade 2: >470 to ≤500 ms
- Grade 3: >500 ms

QTc change from baseline:

- ≥30 to <60 ms
- ≥60 ms

Vital Signs

Pulse:

- abnormally high: ≥120 bpm
- abnormally low: ≤50 bpm

Systolic and diastolic blood pressure[a,b]:

- Grade 1: >120/80 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)

[a] Refer to the DAIDS version 2017

[b] Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

10.14 Appendix 14: Protocol Amendment History

Refer to PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE.

Amendment 2 (18 December 2019)

Overall Rationale for the Amendment: The dose selection of RPV 15 mg qd for participants with a body weight of <25 kg is added CCI [redacted] The appropriateness of RPV 15 mg qd dose for children with body weight <25 kg will be evaluated through the current study TMC278HTX2002 in combination with data obtained in another ongoing pediatric RPV study, TMC278-TiDP38-C213 (C213). In addition, to accommodate regulatory requirements concerning the evaluation of RPV in the pediatric population, the intensive PK data from this study TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥ 11 kg), will be combined with the C213 Cohort 2 (children aged ≥6 to <12 years) data, as available, for the in-study RPV dose evaluation. Approximately 40 participants will be enrolled in the 2 studies combined; at least 12 participants with a body weight of <25 kg, including at least 7 participants with a body weight of <20 kg. Other additional updates are listed below.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3.3 Schedule of Activities for Switch to Adjusted RPV Dose (if Applicable) 4.1 Overall Design 4.3 Justification for Dose 6.1 Study Interventions Administered 6.6.2 Dose Modification (Adjustment) Rules 9.5 Independent Data Monitoring Committee Analyses	The dose selection of RPV 15 mg qd for participants with a body weight of <25 kg is added.	CCI [redacted] The appropriateness of RPV 15 mg qd dose for children with body weight <25 kg will be evaluated through the current study TMC278HTX2002 in combination with data obtained in another ongoing pediatric RPV study, TMC278-TiDP38-C213 (C213).
1.1 Synopsis 1.2 Schema 6.6.1 Dose Evaluation Criteria	Updated to clarify that the intensive PK data from this study TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥ 11 kg), will be combined with the C213 Cohort 2 (children aged ≥6 to <12 years) data, as available, for the in-study RPV dose evaluation. Approximately 40 participants will be enrolled in the 2 studies combined; at least 12 participants with a body weight of <25 kg at baseline, including at least 7 participants with a body weight of <20 kg at baseline.	To accommodate regulatory requirements concerning the evaluation of RPV in the pediatric population.

Section Number and Name	Description of Change	Brief Rationale
1.3.1 General Schedule of Activities 2.3.5 Overall Benefit/Risk Assessment 6.5.3 Disallowed Concomitant Therapy 9.4.3 Safety Analyses 10.2 Appendix 2: Monitoring and Safety for Specific Toxicities 10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV 10.7 Appendix 7: Clinical Laboratory Tests	The ACTH stimulation test on Day 1 and at Week 24 has been removed.	There was no clinically relevant suppression of cortisol secretion and of the adrenal function observed in adults or adolescents aged ≥12 to <18 years in the clinical studies with RPV. Additionally, in the first 9 children aged ≥6 to < 12 years in study C213 treated with RPV +2 N(t)RTIs, there were no AEs related to cortisol abnormalities or signs or symptoms related to clinical manifestations of adrenal insufficiency reported, and no abnormalities in the ACTH stimulation test observed during treatment. Therefore, the performance of the ACTH stimulation test will be limited to cases of confirmed abnormally low cortisol or when signs or symptoms of adrenal insufficiency are observed.
5.2 Exclusion Criteria 11 REFERENCES	The exclusion of 'personal history of asymptomatic arrhythmia' in exclusion criterion #18i), is adapted and the following exclusion criterion is added: *Syncopal episodes if repeated, unexplained, and unrelated to emotional distress.*	Extrasystoles are common in children (20% to 30% in younger children and up to 40% in teenage boys) and occasionally ventricular bigeminy can be seen.[40] Therefore, it is added that personal history of asymptomatic arrhythmias is a reason for exclusion if the asymptomatic arrhythmia is clinically significant in the opinion of the investigator. Syncopal episodes as a risk factor for QTc prolongation (Exclusion criterion #18) was deleted in Amendment 1. This exclusion criterion is now added in a clarified form.
6.5.1 Background Regimen	Added a statement explaining that no dual combination of ARVs are allowed in this study.	Use of DTG as part of a dual combination regimen with RPV is currently under investigation in children and not yet approved. Investigator selected ARVs can only be administered according to the indication approved in the country. Dual combination of ARVs is not allowed in this study.
6.5.2 Allowed Concomitant Therapy 10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV	Updated to clarify that the additional safety monitoring by ECG and the PK sample are only required for participants receiving CYP3A4 inhibitory medications or concomitant medications associated with risk of Torsade de Pointes for >2 days. The requirements for an ECG, and its associated PK sample, before the start of the medication have been removed for use of such disallowed medications ≤2 days and are kept if these medications are going to be used >2 days.	To limit the burden for participants and reduce complexity of the study. No cardiovascular impact is expected with a short period of administration (≤2 days).

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.1 General Schedule of Activities 1.3.3 Schedule of Activities for Switch to Adjusted RPV Dose (if Applicable) 2.1 Study Rationale 2.2 Background 3 OBJECTIVES AND ENDPOINTS 4.3 Justification for Dose 6.1 Study Interventions Administered 8.10.3 Questionnaires	Replaced the term 'dispersible tablet' with '2.5-mg tablet'	To align with the more appropriate technical terminology for this formulation. The tablet composition and intended use have not changed and hence safety and efficacy are not impacted. Tablets still need to be dispersed prior to use.
1.3.1 General Schedule of Activities	Adjusted footnotes for PENTA Adherence Questionnaires in flowchart 1.3.1.: Removed footnote ff and added new footnote ll.	The PENTA Adherence Questionnaires are translated in each local language requested. The PENTA adherence Questionnaire is for children above 6 years of age and for caregivers
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Added secondary endpoint: Proportion of participants with HIV-1 RNA <400 and ≥400 copies/mL using the FDA Snapshot approach through 24 and 48 weeks of study treatment	For completeness
1.2. Schema 1.3.1 General Schedule of Activities 4.1 Overall Design	Added that the retest of abnormal laboratory results or plasma VL/resistance testing, should be captured in this TMC278HTX2002 study if the participants roll over to the TMC278IFD3004 study.	Clarification
1.3.2 Schedule of Activities for Intensive Pharmacokinetic Sampling	Added that the body weight for inclusion in intensive PK sampling is determined at baseline	Clarification
1.3.2 Schedule of Activities for Intensive Pharmacokinetic Sampling 8 STUDY ASSESSMENTS AND PROCEDURES	Adjusted 'approximately 8 mL' to 'approximately 10 mL' total volume intensive PK sampling.	As each tube may draw up to 1.2 mL, the total volume may add up to 9.6 mL
5.1 Inclusion Criteria	Added 'or at least 6 months prior to screening' to inclusion criterion #4	Alignment with section 4.1 Overall Design
5.3 Lifestyle Considerations	Adjusted the lifestyle considerations.	To limit dietary restrictions for HIV infected children and align with other pediatric RPV studies
6.5.1 Background Regimen	'i.e., generics' is corrected to 'or generics'	Correction
6.5.3 Disallowed Concomitant Therapy	Added the exception for the ARVs efavirenz and nevirapine	Clarification
6.6.1 Dose Evaluation Criteria	Added Mini-Cohort Dose Evaluation Criterion	Alignment with study C213

Section Number and Name	Description of Change	Brief Rationale
6.7 Intervention After the End of the Study	Added treatment options after the end of the study: 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.	Alignment with study C213
8.10.3 Questionnaires	Added that site staff provides support to the participant or their parent(s)/caregiver(s) in completing the questionnaires.	Clarification
8.2.1 Physical Examination	Removed 'Subjects should be undressed (underwear is allowed) during these full physical examinations.'	Full physical examination is to be done as per local standard of care
8 STUDY ASSESSMENTS AND PROCEDURES	Adjusted blood volumes	Update to current schedule
8 STUDY ASSESSMENTS AND PROCEDURES	Added Post-Switch Visit time windows	For completeness
8 STUDY ASSESSMENTS AND PROCEDURES	Added 'participants'' before 'representative'	Clarification
1.1 Synopsis 9.4.2 Efficacy Analyses	Removed 'Time-to-event data (ie, time to loss of virologic response) will be graphically presented by means of Kaplan-Meier curves'.	Correction
10.1 Appendix 1: Abbreviations and Trademarks	Definitions for Virologic Response, Virologic Failure, Suspected Virologic Failure and Confirmed Virologic Failure added.	Clarification
10.2 Appendix 2: Monitoring and Safety for Specific Toxicities	Removed the sentence on the investigator manual.	An investigator manual is not being used in this study. The management of rash is described throughout this section in the protocol.
10.2 Appendix 2: Monitoring and Safety for Specific Toxicities	Changed '%248 nmol/L (9 &g/dL)' to '%500 nmol/L (18.1 &g/dL)'	Correction
10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV	Moved telithromycin and troleandomycin up to be included with clarithromycin and erythromycin	To present all macrolide antibiotics together
10.6 Appendix 6: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV	Added the note to Appendix 6 that the list of disallowed concomitant medication and medication to be used with caution is not exhaustive.	Clarification

Section Number and Name	Description of Change	Brief Rationale
10.15 Appendix 15: CDC Growth Charts	The CDC growth charts for Boys and Girls 2-20 years were included in the protocol as an Appendix.	For completeness
Throughout entire document	Including 'approximately' 12 participants with a body weight of <25 kg at baseline was adjusted to 'at least' 12 participants.	Correction
Throughout entire document	Substituted 'subjects' with 'participants'	Current standard language
1.1 Synopsis 8.10.1 Resistance 9.4.2 Efficacy Analyses	Some administrative and editorial adjustments were made	Clarification

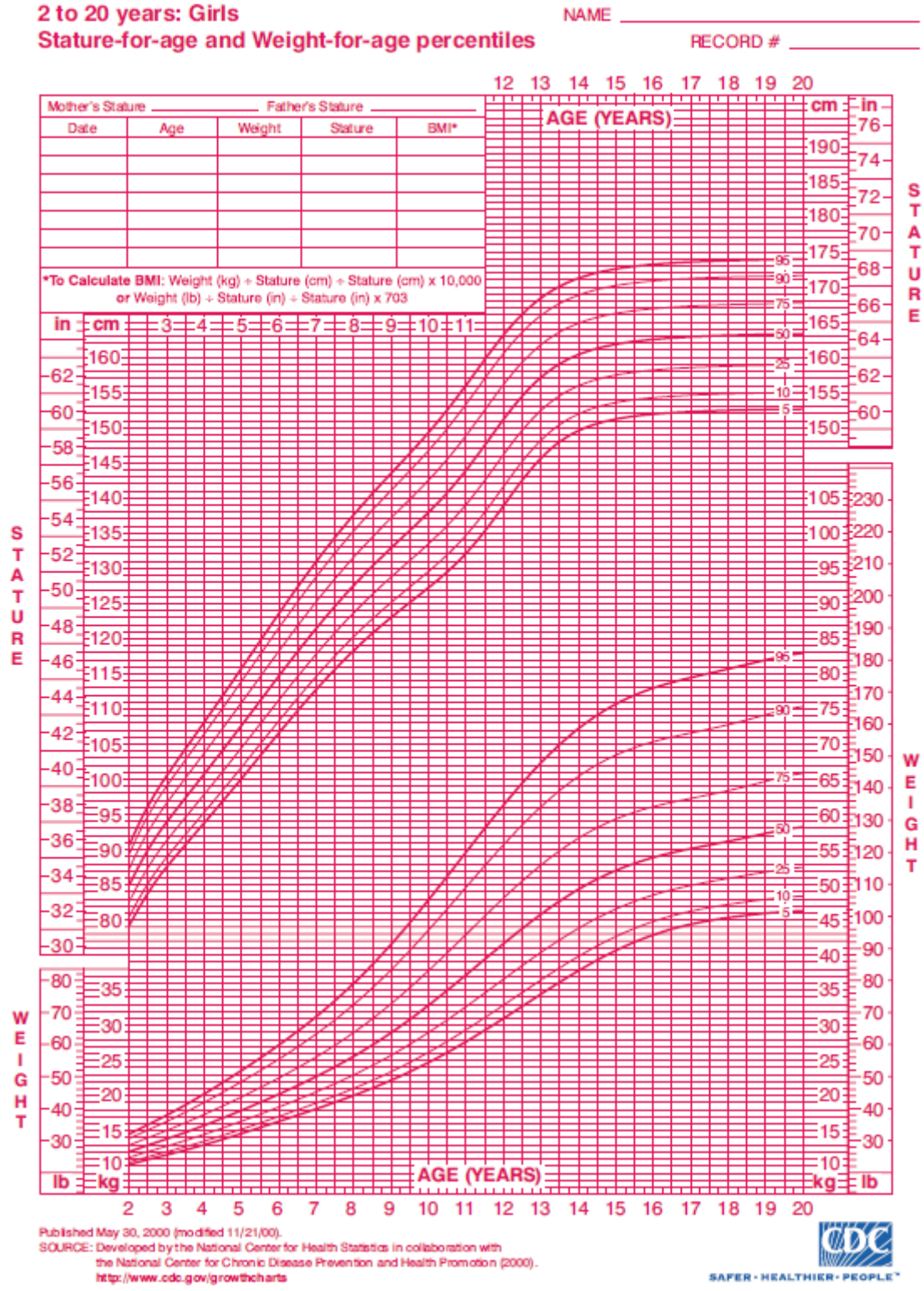
Amendment 1 (24 April 2019)

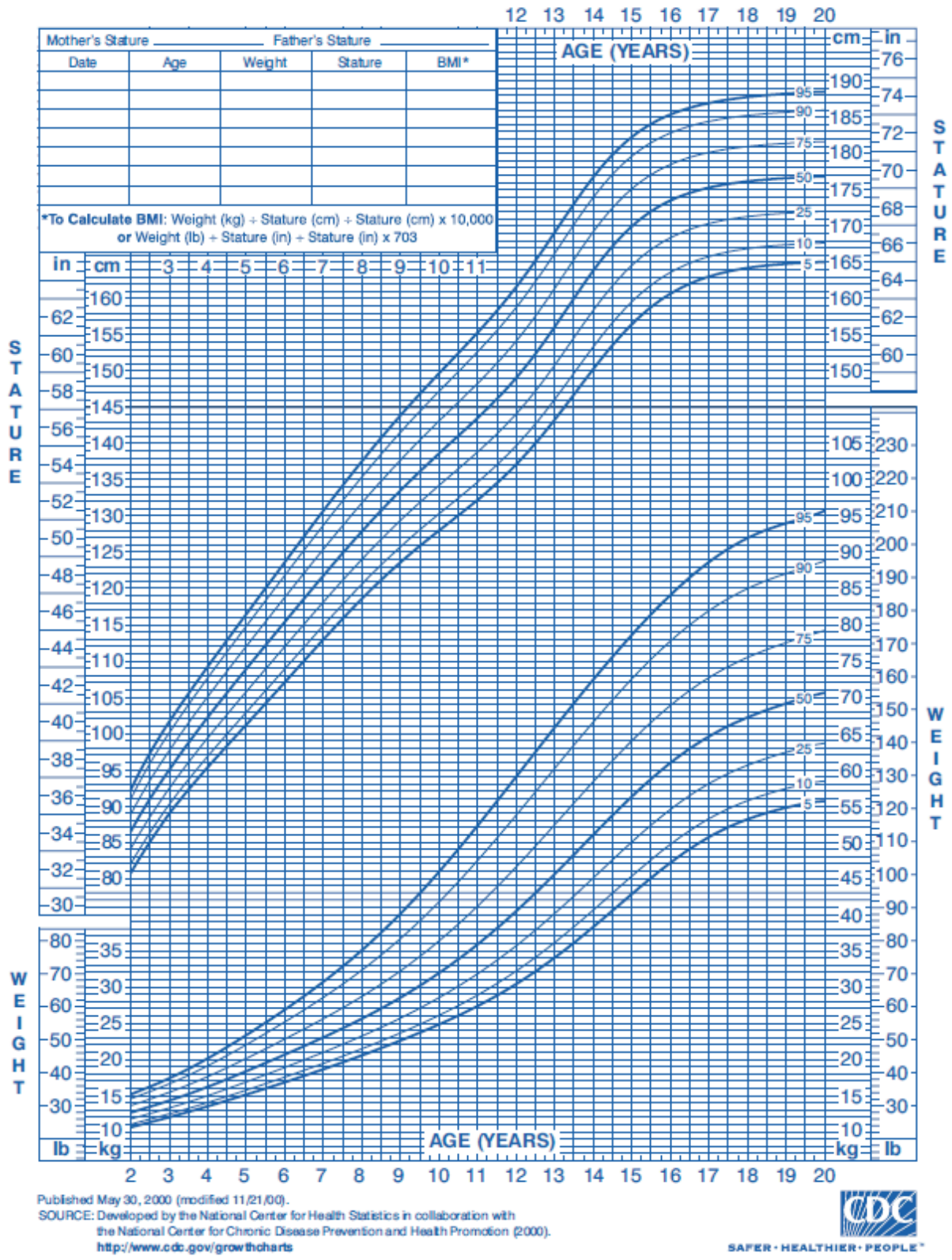
Overall Rationale for the Amendment: Based on local practice in certain countries, children younger than 12 years of age are not consistently informed of their HIV-1 diagnosis. Therefore, inclusion criterion 5 will be removed. Other additional updates are listed below.

Section Number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Inclusion criterion 5 stating that participants need to be aware of their HIV-1 diagnosis was removed.	Based on local practice in certain countries, children younger than 12 years of age are not consistently informed of their HIV-1 diagnosis.
5.1 Inclusion Criteria	Inclusion criterion 4 was modified requiring viral load testing within 2-12 months prior to screening and at screening and allowing 'blips' (single viral load ≥50 HIV-1 RNA copies/mL) during this period.	Not all investigators perform viral load testing every 6 months and blips occur quite regularly (eg due to other illnesses) which is anticipated to limit recruitment.
5.2 Exclusion Criteria	Exclusion criterion 10 was modified to allow treatment with placebo within 90 days prior to screening.	Participants who received placebo treatment in another clinical trial within 90 days prior to screening and who meet all eligibility criteria will be allowed to enter the study immediately.
5.2 Exclusion Criteria	Syncopal episodes were removed from exclusion criterion 18.	Syncopal episodes in children are usually benign.[12] Additionally, in the current study an ECG is performed at Screening and Baseline, and children with clinically significant ECG findings (exclusion criterion 11) and risk factors for QT prolongation (exclusion criterion 18) are excluded from participation in the study.
1.3.1 General Schedule of Activities, 4.1 Overall Design	The requirement to record historical HIV-1 genotyping results in the CRF at screening was added.	Per inclusion criterion 12, sensitivity to RPV and the selected background ARVs should be demonstrated by historical HIV-1 genotyping results at screening for children aged ≥2 to <6 years. It was clarified that the availability of the results and the subtype will be recorded in the CRF. If a historical

Section Number and Name	Description of Change	Brief Rationale
		HIV-1 genotyping result (ie, subtype) is available for children aged ≥6 to <12 years, this should be recorded in the CRF as well and provided to the sponsor.
1.3.1 General Schedule of Activities	The requirement for collecting plasma for genotyping at screening was removed.	Participants need to be virologically suppressed on a stable ARV regimen for at least 6 months at screening.
1.3.1 General Schedule of Activities	The requirement for PK sample collection at W2 was added.	An extra pre-dose sample for PK, 2 weeks after switch to RPV, is considered relevant information.
1.1 Synopsis 4.1 Overall Design 6.7 Intervention After the End of the Study	The requirement for participation to rollover study TMC278IFD3004 was clarified.	Participants will only enroll in the pediatric rollover study TMC278IFD3004 if there is a clinical benefit from treatment with RPV after 48 weeks of treatment in TMC278HTX2002.
10.1 Appendix 1: Abbreviations and Trademarks, 10.7 Appendix 7: Clinical Laboratory Tests	GFR correction factor for children 12 years of age was added	As children <12 years of age are allowed in this study and they will be treated for 48 weeks (potentially becoming ≥12 years during the study), GFR may need to be calculated for children >12 years of age. Therefore, the GFR correction factor for children >12 years of age was added.
10.10 Appendix 10: Pediatric European Network for the Treatment of AIDS (PENTA) Adherence Questionnaire, 10.11 Appendix 11: Palatability Questionnaire, 10.12 Appendix 12: Swallowability Questionnaire	The questionnaires were replaced with updated ones.	Updated questionnaires are available and were included. The PENTA Adherence Questionnaire (Appendix 10) for patients is to be completed by children 6 years of age and older, as younger children are not expected to be able to complete it.
8.10.2 Diaries	An inconsistency/unclarity was corrected.	It was made clear that diary completion is also required in case of dose adjustment.
10.2 Appendix 2: Monitoring and Safety for Specific Toxicities	Removal of requirement for digital pictures.	Rash is a known ADR for RPV. In case of a grade 3-4 rash, urgent clinical evaluation by a dermatologist is required per protocol. The collection of digital pictures for rash in this study is therefore not considered to add relevant information.
10.2 Appendix 2: Monitoring and Safety for Specific Toxicities	An error was corrected.	Minor error was noted.

10.15 Appendix 15: CDC Growth Charts




2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
SAFER · HEALTHIER · PEOPLE™

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INVESTIGATOR AGREEMENT

TMC278 (rilpivirine)

Clinical Protocol TMC278HTX2002 AMENDMENT 3 Clean

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: Janssen Research & Development _____

Signature: PPD _____ Date: PPD

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status:Approved, Date: 22 February 2021