Clinical Trial Protocol Amendment
GEN-X

Project no:	TMC278-TiDP38		
Department:	Clinical R&D	**Nonproprietary name:**	rilpivirine hydrochloride
Status:	Approved	**Issued Date:**	03-FEB-2020
Protocol Title:	A Phase II, open label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine (TMC278) in antiretroviral-naïve HIV-1 infected adolescents and children aged ≥6 to <18 years		
Trial no:	TMC278-TiDP38-C213	**Clinical Phase:**	II
Sponsor	Janssen Research & Development*		

Summary: This is a Phase II, open label, single arm trial to evaluate the pharmacokinetics, safety, tolerability and efficacy of rilpivirine (RPV, previously known as TMC278) 25 mg once daily (q.d.) or an adjusted dose of RPV (q.d.) in combination with an investigator-selected background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs) (zidovudine [AZT], abacavir [ABC], or tenofovir disoproxil fumarate [TDF] in combination with lamivudine [3TC] or emtricitabine [FTC], whichever is approved and marketed or considered local standard of care) in antiretroviral (ARV) treatment-naïve adolescents and children aged ! 6 to <18 years.

The trial will consist of a screening period of maximum 8 weeks, an initial treatment period of 48 weeks, and a post Week 48 treatment extension period of 4 years. **As of Amendment 10**, the post Week 48 treatment extension period of 4 years is removed for Cohort 2, children ≥6 to <12 years of age. Subjects who withdraw from the trial on or before the Week 48 visit or subjects with ongoing (serious) adverse events ([S]AEs), laboratory abnormalities, or viral load increase at the last on-treatment visit in the extension, will be seen for a follow-up visit 4 weeks later. Additional unscheduled visits may be performed for safety/tolerability reasons and for confirmation of plasma viral load results.

Recruitment and analyses of the initial 48-week treatment period will be structured into 2 age cohorts: Cohort 1, adolescents ≥12 to <18 years of age; Cohort 2, children ≥6 to <12 years of age.

Cohort 1 (≥12 to <18 Years of Age):

As of Amendment 10, Cohort 1, adolescents ≥12 to <18 years of age, has been completed. Therefore, all sections related to Cohort 1 are removed from the summary and greyed out from the body of text for ease of reading.

Cohort 2 (! 6 to <12 Years of Age):

To accommodate regulatory requirements concerning the evaluation of RPV in the pediatric population, overall across studies C213 (Cohort 2; children aged ≥6 to <12 years) and TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥11 kg), approximately 40 subjects will be enrolled of which at least 12 subjects with a body weight of <25 kg, including at least 7 subjects with a body weight of <20 kg. The PK data from Cohort 2 will be combined with the data from pediatric study TMC278HTX2002.

The analysis of the first 10 subjects in Cohort 2, including PK modeling and simulation to further assess the RPV pediatric dose based on accumulating data, was discussed with and endorsed by the IDMC. With this, **at the time**

of Amendment 10, the following RPV dose recommendations will apply to newly enrolled subjects:

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

All ongoing subjects in Cohort 2 (who are already in the post Week 48 treatment extension period **at the time of Amendment 10**) will remain on the RPV 25 mg q.d. dose + 2 N(t)RTIs (investigator-selected), until their roll-over to study TMC278IFD3004 has been completed (see addendum 7.11). All newly recruited subjects will start treatment with the weight-appropriate RPV dose stated above + 2 N(t)RTIs (investigator-selected), until they reach a total treatment duration of 48 weeks, or discontinue earlier. If newly recruited subjects, with a body weight of <25 kg, increase in weight such that they require a 25 mg RPV dose, they can change to the 25 mg tablet formulation.

To further evaluate and confirm the RPV dose for subjects with lower body weight, newly enrolled subjects with a body weight of <25 kg require intensive PK evaluation. An overall analysis of the intensive pharmacokinetic data and all available safety, tolerability and antiviral activity/efficacy data will be reviewed by the Sponsor and the IDMC to assess appropriateness of the dose (see section 6.1.1.2.1 for dose evaluation criteria).

- If the results are not deemed satisfactory, and no alternative RPV dose seems feasible, all subjects will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to local standard of care, and Cohort 2 will be stopped.

- If the results are not deemed satisfactory but concerns can be addressed by adjusting the RPV dose (doses of >25 mg q.d. are not allowed) for certain subjects (e.g. up to a certain body weight), those subjects will be switched to an adjusted dose, while those that don't need dose adjustment, will continue their treatment. For all subjects who require an RPV dose adjustment, a 24-hour intensive pharmacokinetic evaluation after 14 to 18 days on the adjusted dose will be performed. After the subjects have been treated with the adjusted RPV dose for at least 4 weeks or discontinued earlier, an analysis of the intensive pharmacokinetic data (after 14 to 18 days of RPV dosing), and all available safety, tolerability and antiviral activity/efficacy data will be reviewed. If, after review of the data, the RPV dose is still not acceptable, the process will be repeated until an acceptable RPV dose is found or it is deemed necessary to stop

	Cohort 2. **Post Week 48 Treatment Extension Cohort 2 (! 6 to <12 Years of Age):** For subjects enrolling in Cohort 2 **as of Amendment 10**, the post Week 48 treatment extension has been removed. Subjects who experience and are expected to continue experiencing clinical benefit from RPV and their background regimen comprising 2 investigator-selected N(t)RTIs at the end of the initial 48-week treatment period, or ongoing subjects who are already in the post Week 48 treatment extension period **at the time of Amendment 10**, may continue treatment (i.e., RPV + 2 N[t]RTIs) in the roll-over study TMC278IFD3004 or switch to locally available RPV (once commercially available AND reimbursed, OR accessible through another source [e.g. access program or government program]), or other locally available RPV-based regimens. **Study Treatment (Cohort 2):** All ongoing subjects in Cohort 2 (who are already in the post Week 48 treatment extension period **at the time of Amendment 10)** will remain on the RPV 25 mg q.d. dose + 2 N(t)RTIs (investigator-selected), until their roll-over to study TMC278IFD3004 has been completed (see addendum 7.11). For newly recruited subjects **as of Amendment 10**, the ART will consist of RPV (weight-based dosing) and an investigator-selected background regimen containing 2 N(t)RTIs. The investigator-selected N(t)RTIs will be AZT, ABC, or TDF in combination with 3TC or FTC, given as the co-formulation or as the separate components, whichever is approved and marketed or considered local standard of care for children aged ! 6 to <18 years in a particular country. Only branded versions of the N(t)RTIs, or generics with tentative US FDA approval and/or WHO prequalified drugs, are to be prescribed by the investigator. If not available, generic drugs approved by the local Health Authorities or drugs procured by the UN international organizations (i.e., UNICEF) can be allowed upon approval by the sponsor.
Investigator:	See local Informed Consent Form
Site Address:	See local Informed Consent Form
Treatment:	48 weeks + post Week 48 treatment extension of 192 weeks, if applicable (excluding max. 8 weeks screening and 4 weeks follow-up).

Protocol History[a] TMC278-TiDP38-C213			
Document Type and *File Name*	**Issue Date**	**Amendement Type**	**Comments**
Initial Clinical Trial Protocol *TMC278-C213-CTP*	12-Aug-2008	-	-
Clinical Trial Protocol Amendment I *TMC278-C213-CTPA-GEN-I*	05-Aug-2009	Substantial	Mainly: Change in withdrawal criteria related to virologic failure, withdrawal of consent and grade 3 or 4 glucose elevations; change in inclusion criterion regarding minimum body weight necessary for inclusion; additional assessments of 17-hydroxyprogesterone, aldosterone, FSH, LH, progesterone, androstenedione, testosterone, DHEAS at Week 12 and 24; no ACTH test to be performed in case of withdrawal from trial because of pregnancy; reduce total volume of blood drawn over the entire trial; update of safety monitoring guidance in case of signs/symptoms of adrenal insufficiency; additional measurement of CD4+ cell count at Week 12; follow-up visit necessary in case of ongoing AEs at Week 48 or early withdrawal from the trial; optional 4-year extension of RPV treatment after Week 48; height no longer determined at all visits; terminology of glomerular filtration rate to be used instead of creatinine clearance; correct mistake in NNRTI list in exclusion criterion; specification that the data monitoring committee will not include Sponsor representatives, only external experts; Other minor corrections for accuracy, consistency, clarification.
First Revised Clinical Trial Protocol *TMC278-C213-CTP-v2*	05-Aug-2009	-	Integrates the Initial CTP and CTPA GEN I.

[a] This overview lists general amendments to the protocol only. Site and country specific amendments to the protocol are not included.

Protocol History[a] TMC278-TiDP38-C213			
Document Type and *File Name*	**Issue Date**	**Amendement Type**	**Comments**
Clinical Trial Protocol Amendment II *TMC278-C213-CTPA-GEN-II*	20-May-2010	Substantial	This amendment implements following changes: It allows subjects to switch to a weight-adjusted dose, if needed, it allows tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) as investigator-selected background regimen and it aligns changes with the latest EMA Decision on the Pediatric Investigational Plan (PIP).
Second Revised Clinical Trial **Protocol** *TMC278-C213-CTP-v3*	10-Sep-2010	-	Integrates the First Revised CTP and CTPA GEN II.
Clinical Trial Protocol Amendment III *TMC278-TiDP38-C213-CTPA-GEN-III*	29-Jun-2011	Substantial	This amendment implements the following changes: a 4-year post Week 48 treatment extension provided through this trial; first part of this trial covers Part 1a and Part 1b to collect pharmacokinetic, safety, and efficacy data in a small cohort before proceeding with Part 2; change in inclusion criterion with regards to baseline viral load; update of Phase IIb and Phase III data in adults; option to prolong the screening period; clarification that N(t)RTI combinations other than ABC/3TC, AZT/3TC, and TDF/FTC are allowed; treatment adherence counseling (and checking of adherence if applicable) required at every visit; update of time points for statistical analyses; administrative and textual changes and corrections.
Third Revised Clinical Trial Protocol *TMC278-C213-CTP-v4*	06-Jul-2011	-	Integrates the Second Revised CTP and CTPA GEN-III.
Clinical Trial Protocol Amendment IV *TMC278-C213-CTPA-GEN-IV*	02-Feb-2012	Non-Substantial	See Protocol Amendments Section for details.
Clinical Trial Protocol Amendment V *TMC278-C213-CTPA-GEN-V*	29-Aug-2013	Non-Substantial	See Protocol Amendments Section for details.
Clinical Trial Protocol Amendment VI *TMC278-C213_Protocol_Amend_6*	08-Oct-2015	Substantial	See Protocol Amendments Section for details.

Protocol History[a] TMC278-TiDP38-C213			
Document Type and *File Name*	**Issue Date**	**Amendement Type**	**Comments**
Clinical Trial Protocol Amendment VII *TMC278-C213_Protocol_Amend_7*	18-Dec-2015	Substantial	See Protocol Amendments Section for details.
Clinical Trial Protocol Amendment VIII *TMC278-C213_Protocol_Amend_8*	01-Dec-2016	Substantial	See Protocol Amendments Section for details.
Clinical Trial Protocol Amendment IX *TMC278-C213_Protocol_Amend_9*	20-Mar-2018	Substantial	See Protocol Amendments Section for details.
Clinical Trial Protocol Amendment X *TMC278-C213_Protocol_Amend_10*	This document	Substantial	See Protocol Amendments Section for details.

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PROTOCOL AMENDMENTS

Amendment GEN-X (Issued Date: 12 December 2019)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.
The overall reason for the amendment: The initial RPV dose selected for all subjects, including children aged ≥6 to <12 years, was 25 mg q.d. Based on accumulating data a new dose has been selected for this subgroup. This amendment is created to include the recommended RPV dose of 15 mg q.d. for children aged ≥6 to <12 years (Cohort 2) with a body weight of <25 kg. Subjects already enrolled before the implementation of this amendment will remain on their original RPV dose of 25 mg q.d. Other changes are described in the rationales below and are all applicable to Cohort 2 only, as Cohort 1 (adolescents) has already been completed.
Description of Change(s)
Rationale: Based on all the available PK data for RPV at the time of Amendment 10, it was determined through modeling and simulation that children with a body weight of <25 kg should be dosed with RPV 15 mg q.d. and children with a body weight of ≥25 kg should be dosed with RPV 25 mg q.d. The appropriateness of RPV 15 mg q.d. dose for children with body weight <25 kg will be evaluated through the current study in combination with data obtained in another ongoing pediatric RPV study TMC278HTX2002 (see further). For subjects with a body weight of ≥25 kg, sufficient intensive PK data have been gathered. Therefore, for new subjects with a body weight of ≥25 kg no further intensive PK sampling is needed, and these subjects can follow the Cohort 2 visit schedule with sparse PK sampling only. For subjects on the RPV 15 mg q.d. dose, intensive PK data are needed for further dose evaluation and confirmation. Therefore, subjects with body weight <25 kg will undergo an intensive PK visit after 2 weeks (Day 14-18) of treatment (see section 2.2.2) and, if the dose is appropriate and no further adjustment is needed according to the dose evaluation criteria described in section 6.1.1.2.1, they can continue the Cohort 2 visit schedule.

	Summary
	2.2.1.2. Flowchart for Switch to Adjusted Dose in Cohort 2
	2.2.2. Flowchart for Intensive Pharmacokinetic Sampling in Cohort 2
	3.2. Cohort 2: Pediatric Subjects Aged ≥6 to <12 Years
	4. Introduction
	5. Objectives
	6.1.1.2. Cohort 2: Children Aged ≥6 to <12 Years
	6.1.1.2.1 Dose Evaluation Criteria for Cohort 2
	6.1.2.2. Cohort 2: Children Aged ≥6 to <12 Years
	6.3.1. Identity of Investigational Product
	6.3.3. Dosage and Treatment Overview Per Subject
	6.4.12. Assessment of Palatability of RPV Formulation
	6.5 Monitoring and Safety for Specific Toxicities
	6.6.2.4 Pharmacokinetic Parameter Analyses

	7.11. Addendum 11: Pharmacokinetic Modeling for Cohort 2 Dose Selection
Rationale: It is clarified that, to accommodate regulatory requirements concerning the evaluation of RPV in the pediatric population, overall across studies C213 (Cohort 2; children aged ≥6 to <12 years) and TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥11 kg), approximately 40 subjects will be enrolled of which at least 12 subjects with a body weight of <25 kg, including at least 7 subjects with a body weight of <20 kg. The PK data from Cohort 2 will be combined with the data from pediatric study TMC278HTX2002.	
	Summary
	6.1.2.2. Cohort 2: Children Aged ≥6 to <12 Years
	6.3.9 Independent Data Monitoring Committee
	6.6.1.2. Cohort 2: Children Aged ≥6 to <12 Years
Rationale: The requirement for a 4-year follow-up period in this study for subjects enrolled in Cohort 2, has been removed from the Pediatric Investigational Plan (PIP) by the Pediatric Committee (PIP Decision P/0322/2018, dated 12 September 2018). Therefore the 4-year follow-up is removed from this C213 study and subjects are offered to continue treatment with RPV through a roll-over study or to switch to locally available medication.	
	Summary
	2.2.1. Flowchart for all Assessments in Cohort 2 (Screening, Initial Treatment Period, Post Week 48 Treatment Extension, and Follow-up)
	2.2.1.3. Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up)
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	6.3.2. Other Medication Administered in the Trial
	6.4.1. Timing of Assessments
	6.4.2. Time Windows
	6.6 Statistical Methods Planned and Determination of the Sample Size
Rationale: The ACTH stimulation test at Day 1 and Week 24 has been removed because no clinically relevant suppression of cortisol secretion and of the adrenal function was observed in adults or adolescents aged ≥12 to <18 years (Cohort 1) in the clinical studies with RPV. Additionally, in the first 9 children aged ≥6 to < 12 years in Cohort 2 of this study 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.	
	2.1.1 Flowchart for All Assessments in Cohort 1 (Screening, Initial Treatment Period, Post Week 48 Treatment Extension, and Follow-up)
	2.2.1.3. Flowchart for Assessments From Week 8 Onwards in Cohort 2

(Initial Treatment Period From Week 8 Onwards, and Follow-up)
6.3.13.1. Disallowed Concomitant Medication
6.4.9.2.3.2. Cohort 2: Children Aged ≥6 to <12 Years
6.6.2.5.2 Clinical Laboratory Tests
Rationale: The section 'Disallowed Concomitant Medication' has been adjusted to clarify that the additional safety monitoring by ECG and the PK sample are only required for subjects receiving CYP3A4 inhibitory medications or medications associated with risk of Torsade de Pointes for >2 days, as no cardiovascular impact is expected with a period of administration of ≤2 days. Therefore, in order to limit the burden for subjects and reduce complexity of the study, the requirements for an ECG, and its associated PK sample, before the start of the medication have been removed for use of such medications ≤2 days, and are kept if these aformentioned medications are used >2 days.
6.3.13.1. Disallowed Concomitant Medication
6.5 Monitoring and Safety for Specific Toxicities
Rationale: The exclusion of "personal history of asymptomatic arrhythmia" and of "syncopal episodes" (exclusion criterion #19, Risk factors for QTc prolongation) is adapted. 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.[60] Also syncopal episodes in children are not uncommon and are usually benign[61] and not associated with cardiac pathology. 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, and syncopal episodes are a reason for exclusion if repeated, unexplained, and unrelated to emotional distress.
6.2.3. Exclusion Criteria
CCI [redacted]
6.3.1 Identity of Investigational Product
6.4.12 Assessment of Palatability of RPV Formulation
Rationale: The requirement for digital pictures has been removed. 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.
6.5.1. Cutaneous Event/Rash
7.3. Addendum 3: Visit Schedule for Cutaneous Reaction/Rash Follow-up
Rationale: Efficacy parameters TLOVR-based response rates and change in $\log_{10}$ plasma viral load have been removed as these endpoints are no longer reported in HIV clinical trials as they are superseded by the Snapshot approach.
6.6.2.2.1. Plasma viral load
Rationale: Some administrative and editorial adjustments were made.

"i.e., generics" corrected to "or generics"	Summary 6.2.5. Removal of Subjects from Therapy or Assessment #5 6.3.3.Dosage and Treatment Overview Per Subject 6.3.5. Individually Selected Background Regimen 6.5.11.3. Hypersensitivity Reactions

Abbreviations ADR, HLA, PK and VL added. Definition for 'Suspected Virologic Failure' added for alignment with PIP. Definition for 'Virologic Response' removed from Loss of Response description and added independently.	1. Glossary
Clarified that the retest of abnormal laboratory results or plasma VL/resistance testing should be captured in this C213 study if the participant rolls over to the TMC278IFD3004 study.	2.2.1.3 Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up) 3.2 Cohort 2: Pediatric Subjects Aged ≥6 to <12 Years 6.1.1.2 Cohort 2: Children Aged ≥6 to <12 Years 6.2.5 Removal of Subjects From Therapy or Assessment
Added 'at least' and 'approximately' to the blood volumes to be collecte as each tube may draw up to 1.2 mL and the total volume may add up to 9.6 mL	2.2.2. Flowchart for Intensive Pharmacokinetic Sampling in Cohort 2
Clarified that site staff provides support to the subject or their parent(s)/caregiver(s) in completing the questionnaires.	6.3.12. Adherence
Added a note to Table 1 clarifying that the list of disallowed concomitant medication and medication to be used with caution is not exhaustive.	6.3.13.1. Disallowed Concomitant Medication
Added Post Switch Visit time windows for completion.	6.4.2 Time Windows
Alignment with PIP: Adjusted 'Virologic Failure' to 'Suspected Virologic Failure' and added the fact that deep sequencing may be performed.	6.4.7. Resistance Determinations
Editorial error corrected	6.4.8. Pharmacokinetic Evaluations
Removed 'Subjects should be undressed (underwear is allowed) during these full physical examinations', as the full physical examination is to be done as per local standard of care.	6.4.9.4. Physical Examination
248 nmol/L corrected to 500 nmol/L	6.5.5.2. Cohort 2: Children Aged ≥6 to <12 Years
The obligatory withdrawal from the study for renal complications is removed and 'must be' has been adjusted to 'may be'. As these renal complications refer to specific toxicities with concomitant ARV N(t)RTIs used in the study, management of a decrease in eGFR is	6.2.5 Removal of Subjects From Therapy or Assessment 6.5.11.5. Renal Complications

up to the investigator.

Amendment GEN-IX (Issued Date: 20-Mar-2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment is created to update the in- and exclusion criteria to facilitate patient recruitment since the study target population has become scarce. Through this amendment, enrollment of subjects ≥6 to <12 years of age who have a history of receiving a single dose of nevirapine (sdNVP) for prevention of mother-to-child transmission (PMTCT) in Cohort 2 of the study will be allowed. The evolution of proviral genotype will be assessed at screening and Week 48 and virologic response will be closely monitored during the treatment period.

Description of Change(s)

Rationale: In order to facilitate patient recruitment, the protocol in- and exclusion criteria are adjusted to allow enrollment in Cohort 2 of subjects ≥6 to <12 years of age who previously received a sdNVP for PMTCT. In Cohort 1 of the study, subjects who received sdNVP for PMTCT were enrolled. In Cohort 1, 8/36 subjects experienced virologic failure, however, data on PMTCT use at time of birth were either not available (13/30, 43.3%) or it was reported that no PMTCT was used (17/30, 56.7%).[a] The emerging mutations observed in these subjects with virologic failure were previously identified in the RPV Phase 3 adult studies. Virologic failure was generally associated with the emergence of RPV resistance-associated mutations (RAMs), most commonly E138K, in combination with NRTI RAMs, most commonly M184V. Given the virologic failures observed in Cohort 1, subjects who previously received sdNVP for PMTCT were not allowed in Cohort 2 at the time of implementation of Amendment 6. The reason for the virologic failures observed in Cohort 1 is now considered most probably not related to the use of sdNVP for PMTCT because the observed resistance patterns were in line with those observed in Phase 3 in adults and because the data on PMTCT use at time of birth were either not available or no PMTCT was used. Moreover, most virologic failures (6/8) occurred in Uganda where PMTCT was not widely adopted at the time the Ugandan study participants were infected.

The main reasons for adapting the in- and exclusion criteria in terms of prior sdNVP use for PMTCT are:

1. Infeasibility of recruitment:
   Because of the successful global adoption of PMTCT regimens[b], pediatric patients naïve to sdNVP or zidovudine (AZT) use for the PMTCT have become increasingly scarce. The Joint United Nations Program on human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (UNAIDS) reported that coverage of antiretroviral programs for PMTCT increased from 57% in 2011 to 73% in 2014 among their 22 priority countries.

   In June 2016, the World Health Organization (WHO) issued updated HIV-exposed infant prophylaxis guidelines, stating that infants born to mothers with HIV who are at high risk of acquiring HIV should receive dual prophylaxis with AZT twice daily and NVP once daily for the first 6 weeks of life (whether they are breastfed or formula fed). Prior to 2012, the PMTCT treatment for infants consisted almost exclusively of sdNVP. As patients in the age range to be enrolled in Cohort 2 (≥6 to <12 years) would have

[a] Stevens M, Vanveggel S, Hoogstoel A et al. A Phase II open-label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of TMC278 in antiretroviral-naïve HIV-1 infected adolescents aged 12 to <18 years. Janssen Infectious Diseases – Diagnostics BVBA. TMC278-TiDP38-C213 Clinical Study Report Week 48 Analysis. Issued date: 18 December 2014.

[b] Joint United Nations Programme on HIV/AIDS (UNAIDS). 2014 Progress report on the global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva, Switzerland, 2014. Available at http://www.unaids.org/sites/default/files/documents/JC2681_2014-Global-Plan-progress_en.pdf. Accessed

been born in 2012 or before, it is likely they received sdNVP, making recruitment impracticable.

2. Archived resistance:
The strongest predictor for carrying NNRTI mutations after PMTCT exposure is young age.[c] The probability for otherwise treatment-naïve children to have resistance due to sdNVP use at birth decreases with age as resistance against NVP typically declines over time towards frequencies below the detection threshold of sequencing assays.[c,d,e] The decreased incidence of NNRTI resistance in individual infants has been confirmed by multiple studies, showing the fading of sdNVP-induced mutations over 12 months after infection. Studies with longer individual follow-up time are rare, but a recent study investigated the persistence of NNRTI resistance up to 32 months of age using deep sequencing and showed that certain NNRTI RAMs can persist without decay over a median of 13 months (interquartile range [IQR] 12-16) to a median of 21 months of age (IQR 17-32).[f] The persistence of NNRTI resistance is likely highest for infants and children <2 years of age and it is anticipated that prevalence will further decrease with age.

In subjects who have received sdNVP for PMTCT and who will be allowed to enroll in Cohort 2 after implementation of the current Amendment 9, the presence of archived NNRTI or NRTI resistance cannot be fully excluded. Archived resistance is difficult to assess with accuracy and the current methods are generally used for exploratory research. Nonetheless, the sponsor will collect peripheral blood mononuclear cells (PBMCs) at screening to retrospectively evaluate the presence of RAMs in children enrolled in Cohort 2 after the implementation of Amendment 9. To assess whether this could have had an impact on response to the study regimen, the evolution of proviral genotype will be assessed at screening and Week 48 and virologic response will be closely monitored during the treatment period. No human DNA analysis will be performed on these samples. Given the exploratory nature of the assessment and the large number of assessments and extensive blood sampling at the baseline visit, the reference PBMC sample will be taken at screening.

	1 Glossary
	2.2.1.1 Flowchart for Assessments up to Week 4 in Cohort 2 (Screening and Initial Treatment Period up to Week 4)
	2.2.1.3 Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up)
	6.1.1.2 Cohort 2: Children Aged ≥6 to <12 Years
	6.2.2 Inclusion Criteria
	6.2.3 Exclusion Criteria
	6.4.7 Resistance Determinations
	6.6.2.3 Resistance Determinations

[c] Kuhn L, Hunt G, Technau KG, et al. Drug resistance among newly-diagnosed HIV-infected children in the era of more efficacious antiretroviral prophylaxis. AIDS. 2014;28(11):1673-1678.

[d] Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET012). AIDS. 2011;15(15):1951-1957.

[e] Loubster S, Balfe P, Sherman G, et al. Decay of K103N mutants in cellular DNA and plasma RNA after single-dose nevirapine to reduce mother-to-child HIV transmission. AIDS. 2006,20(7):995-1002.

[f] Kanthula R, Beck I, Van Dyk G, et al. Persistance of HIV drug resistance in children exposed to nevirapine prophylaxis. CROI 2016. Poster 847.

Rationale: The main PK analyses to characterize the RPV PK properties in children are conducted at the time of the Week 4, Week 24 and Week 48 analyses. Pharmacokinetic samples taken at a later time point are not anticipated to have a significant impact on the findings/conclusions of the Week 24/48 PK analyses. Therefore, for Cohort 2, no PK sample will be taken beyond Week 48 and the assessment at Week 240 is deleted from the flowchart.
2.2.1.3 Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up)
Rationale: The introduction was updated to indicate that, at the time of the Amendment 9 writing, rilpivirine (RPV) was approved in several countries, including USA and Europe, in adolescents ≥12 years of age.
4 Introduction
Rationale: The definition of an abnormal ACTH stimulation test as defined for Cohort 2 was corrected: “the cortisol value after ACTH stimulation is <500 nmol/L” instead of "all cortisol values prior to and after ACTH stimulation are <500 nmol/L”.
2.2.1.3 Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up)
6.2.5 Removal of Subjects From Therapy or Assessment
6.4.9.2.3.2 Cohort 2: Children Aged ≥6 to <12 Years
Rationale: Section 6.4.1 Timing of Assessments of the protocol has been aligned with Section 6.4.8 Pharmacokinetic evaluations regarding the planning of an unscheduled visit for repeat PK sampling. Moreover, the Time and Events schedule has been aligned with Section 6.4.1 Assessments: following the Week 240 study visit, unscheduled visits may be scheduled in order to follow-up on safety concerns ([S]AEs, laboratory abnormalities and increase in viral load) and to allow retesting of parameters as described in Section 6.4.1.
Summary
2.2.1.3 Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up)
3.2 Cohort 2: Pediatric Subjects Aged ≥6 to <12 Years
6.2.5 Removal of Subjects From Therapy or Assessment
6.4.1 Timing of Assessments
Rationale: It is clarified in the protocol that study visits should be scheduled relative to the baseline visit (Day 1), eg, the Week 1 visit should be scheduled on Day 8 (Day 1 + 7 days) ± the allowed time windows as specified in Section 6.4.2.
2.2.1.1 Flowchart for Assessments up to Week 4 in Cohort 2 (Screening and Initial Treatment Period up to Week 4)
2.2.1.3 Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up)
6.4.2 Time Windows
Rationale: Some clarifications were added and editorial errors and inconsistencies were corrected.
6.1.1.2 Cohort 2: Children Aged ≥6 to <12 Years
6.1.1.2.1 Dose Evaluation Criteria for Cohort 2

Amendment GEN-VIII (Issued Date: 01-Dec-2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Based on local practice and availability of antiretrovirals (ARVs) in certain countries, the protocol requires adjustments to allow the prescription of WHO prequalified drugs. If not available, the use of generic drugs approved by the local Health Authorities or drugs prescribed by the UN international organizations can be acceptable as nucleotide analog reverse transcriptase inhibitor (N(t)RTI) background medication. The inclusion criterion regarding the start of treatment is updated to reflect the new WHO guideline on the start of ARV therapy. Additionally, the criterion for withdrawal after a total cumulative duration of treatment interruptions for suspected toxicities is further clarified per study period instead of over the entire study duration. Other minor changes are described in the rationales below.

Description of Change(s)
Rationale: The protocol requires adjustments to allow the prescription of WHO prequalified drugs, based on local practice and availability of ARVs. If not available, the use of generic drugs approved by the local Health Authorities or drugs prescribed by the UN international organizations can be acceptable as N(t)RTI background medication.
6.1.1.1 Cohort 1: Adolescents Aged ≥12 to <18 Years
6.2.5 Removal of Subjects From Therapy or Assessment
6.3.3 Dosage and Treatment Overview Per Subject
6.3.5 Individually Selected Background Regimen
6.3.13.2 Disallowed Antiretroviral Medication
6.5.11.3 Hypersensitivity Reactions
Rationale: The criterion for withdrawal after a total cumulative duration of treatment interruptions for suspected toxicities was further clarified as applying cumulatively for a time frame of 48 weeks, and not cumulatively over the entire 240 weeks of the study.
6.1.1.1 Cohort 1: Adolescents Aged ≥12 to <18 Years
6.2.5 Removal of Subjects From Therapy or Assessment
6.3.5 Individually Selected Background Regimen
6.5 Monitoring and Safety for Specific Toxicities
Rationale: The minimum number of subjects in Part 2 of Cohort 2 was updated to 25, in line with the Pediatric Investigation Plan Decision P/0012/2016 dated 29 January 2016.
Summary
3.2 Cohort 2: Pediatric Subjects Aged ≥6 to <12 Years
6.1.1.2 Cohort 2: Children Aged ≥6 to <12 Years
6.2.1.2 Cohort 2: Children Aged ≥6 to <12 Years
Rationale: In 2016, WHO released "Consolidated Guidelines on The Use of Antiretroviral Drugs for Treating and Preventing HIV Infection"[59]. The guidelines recommend that antiretroviral therapy (ART) should be initiated in all children living with HIV, regardless of WHO clinical stage or at any $CD4^+$ cell count. Therefore, the word "chronic" was removed in Inclusion criterion #3. Additionally, the Note in Inclusion criterion #8 became outdated and was removed. Subjects with acute HIV infection are still excluded from the study.

6.2.2 Inclusion Criteria
Rationale: The eGFR for subjects aged 22 years and older will be calculated by the MDRD equation as the currently used formula is validated up until 21 years of age.
6.4.9.2.2 Biochemistry
6.5.11.5 Renal Complications
CCI [redacted]
6.3.1 Identity of Investigational Product
Rationale: The wording on final analysis of Cohort 1 and Cohort 2 was adjusted to clarify that there will be 2 final analyses, one for each cohort.
6.6 Statistical Methods Planned and Determination of the Sample Size
CCI [redacted]
6.3.1 Identity of Investigational Product
Rationale: Minor corrections were made.
6.3.5 Individually Selected Background Regimen
6.3.9 Independent Data Monitoring Committee
Rationale: The Janssen Research & Development disclaimer on the frontpage was updated.
Frontpage

Amendment GEN-VII (Issued Date: 18-Dec-2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Based on local practice in certain countries, children younger than 12 years of age are not consistently informed of having HIV infection. Therefore inclusion criterion 3 will be updated to remove the requirement that children enrolled in the study are aware of their HIV status. Children that are unaware of their HIV status, but comply with all other inclusion and exclusion criteria are nevertheless allowed to participate in the study.

Description of Change(s)	Applicable Section(s)
Rationale: See above	
	6.2.2 Inclusion Criteria
Rationale: An ECG assessment after at least 4 weeks of treatment with RPV (initial dose or adjusted dose) is not necessary. An ECG is required after at least 2 weeks of treatment with RPV, when RPV plasma concentrations are at steady-state (steady-state plasma concentrations of RPV are usually reached within 11 days of dosing). This Week 2 ECG assessment is adequate to assess potential safety concerns. The ECG at the 4-weeks Post Switch Visit (in case of switch to a RPV adjusted dose) is therefore removed (in line with assessments for the initial RPV dose)	
	2.2.1.2 Flowchart for Switch to Adjusted Dose in Cohort 2, Part 1 Only (If Applicable)

Amendment GEN-VI (Issued Date: 08-Oct-2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The protocol which was originally designed to include adolescents of ≥12 to <18 years of age has been amended to also include children of ≥6 to <12 years of age.

Description of Change(s)	Applicable Section(s)
Rationale: An additional cohort (Cohort 2) of children of ≥6 to <12 years of age has been added to the current study design in order to collect data on short-term and long-term pharmacokinetics, safety, tolerability, and antiviral activity/efficacy of rilpivirine (RPV) in this additional pediatric age group. In this cohort, treatment-naïve human immunodeficiency virus - type 1 (HIV-1) infected subjects with HIV RNA ≤100,000 copies/mL of ≥6 to <12 years of age will be allowed to enter. The subjects will be treated with RPV 25 mg once daily (q.d.) or an adjusted dose for a maximum of 240 weeks. The primary and final endpoints are Week 48 and Week 240, respectively.	

	Title Page Summary 2 Flowchart 3 Overview of Trial Design 4 Introduction 5 Objectives 6.1.1 Overview of Trial 6.1.2 Discussion of Trial Design and Selection of Dose(s) in the Trial 6.2.1 Sample Size 6.2.2 Inclusion Criteria 6.2.3 Exclusion Criteria 6.2.4.2 Restrictions 6.2.5 Removal of Subjects From Therapy or Assessment 6.3.1 Identity of Investigational Product 6.3.2 Other Medication Administered in the Trial 6.3.3 Dosage and Treatment Overview Per Subject 6.3.4 Timing of Dosing 6.3.5 Individually Selected Background Regimen 6.3.9 Independent Data Monitoring Committee 6.3.12 Adherence 6.3.13.1 Disallowed Concomitant Medication 6.4.1 Timing of Assessments 6.4.2 Time Windows 6.4.7 Resistance Determinations 6.4.8.1 Sample Collection and Handling 6.4.9.2.2 Biochemistry 6.4.9.2.3 Endocrine Assessments 6.4.12 Assessment of Palatability of RPV Formulation (Other Than Tablet Formulation) 6.5 Monitoring and Safety for Specific Toxicities 6.5.5 Signs and Symptoms of Adrenal Insufficiency 6.6 Statistical Methods Planned and Determination of the Sample Size 6.6.1 Determination of Sample Size 6.6.2.2.1 Plasma viral load 6.6.2.4 Pharmacokinetic Parameter Analyses 6.6.2.5.2 Clinical Laboratory Tests 7 References 7.11 Addendum 11: Pharmacokinetic Modeling for Cohort 2 Dose Selection 5.1 Reporting
Additional section headings have been added for clarity	Throughout the protocol
Rationale: The following clarification related to safety monitoring was added: - evaluation of individual growth and pubertal development will also be done by the Independent Data Monitoring Committee (IDMC)	
	6.3.9 Independent Data Monitoring Committee

Rationale: In the adolescent cohort (Cohort 1), corrections were made to the statistical analyses, a Week 240 objective was added, and the wording regarding resistance determination was simplified. In addition, minor corrections were made to the description of the conduct of the trial.	
Changes were made to the statistical analyses	6.6.2.2.1.1 Analysis 6.6.2.2.2 Immunology 6.6.2.5.1 Adverse Events/HIV-Related Events 6.6.2.5.3 Cardiovascular Safety 6.6.2.5.4 Physical Examination
An additional objective was added (240-week evaluation objective)	5 Objectives
Wording regarding resistance determination was simplified	2.1.1.1 Flowchart for Assessments up to Week 4 in Cohort 1 (Screening and Initial Treatment Period up to Week 4) 2.1.1.2 Flowchart for Switch to Weight-adjusted Dose in Cohort 1, Part 1 Only (if applicable) 2.1.1.3 Flowchart for Assessments from Week 8 onwards in Cohort 1 (Initial Treatment Period from Week 8 onwards, Post Week 48 Treatment Extension, and Follow-up) 6.4.7 Resistance Determinations
Minor corrections were made	Summary 2.1.2 Flowchart for Intensive Pharmacokinetic Sampling in Cohort 1, Part 1 Only 6.1.1.1 Cohort 1: Adolescents Aged ≥12 to <18 Years
Rationale: The most recent version of the IB has been referenced and all applicable text has been updated.	
	Summary 4 Introduction 6.3.13.1 Disallowed Concomitant Medication 6.5.11.5 Renal Complications 7 References

	Title Page Summary 2 Flowchart 3 Overview of Trial Design 4 Introduction 5 Objectives 6.1.1 Overview of Trial 6.1.2 Discussion of Trial Design and Selection of Dose(s) in the Trial 6.2.1 Sample Size 6.2.2 Inclusion Criteria 6.2.3 Exclusion Criteria 6.2.4.2 Restrictions 6.2.5 Removal of Subjects From Therapy or Assessment 6.3.1 Identity of Investigational Product 6.3.2 Other Medication Administered in the Trial 6.3.3 Dosage and Treatment Overview Per Subject 6.3.4 Timing of Dosing 6.3.5 Individually Selected Background Regimen 6.3.9 Independent Data Monitoring Committee 6.3.12 Adherence 6.3.13.1 Disallowed Concomitant Medication 6.4.1 Timing of Assessments 6.4.2 Time Windows 6.4.7 Resistance Determinations 6.4.8.1 Sample Collection and Handling 6.4.9.2.2 Biochemistry 6.4.9.2.3 Endocrine Assessments 6.4.12 Assessment of Palatability of RPV Formulation (Other Than Tablet Formulation) 6.5 Monitoring and Safety for Specific Toxicities 6.5.5 Signs and Symptoms of Adrenal Insufficiency 6.6 Statistical Methods Planned and Determination of the Sample Size 6.6.1 Determination of Sample Size 6.6.2.2.1 Plasma viral load 6.6.2.4 Pharmacokinetic Parameter Analyses 6.6.2.5.2 Clinical Laboratory Tests 7 References 7.11 Addendum 11: Pharmacokinetic Modeling for Cohort 2 Dose Selection 5.1 Reporting
Additional section headings have been added for clarity	Throughout the protocol

Rationale: Wording from the most recent protocol template has been incorporated in this document.
Note: Some of the changes may have an effect on study procedures of both cohorts while other changes may not be applicable to Cohort 1 (currently already beyond Week 48) because they are related to e.g., study start-up procedures.

Text related to the following has been revised:	
- Labeling of sample tubes	6.4.3 Handling of Biological Samples
- Collection of questionnaires	6.3.12 Adherence
- Definition of (serious) adverse events [(S)AEs]	6.4.10 Adherence Questionnaire 1.1 Definitions
- Reporting of (S)AEs.	1.4 Reporting of AEs and HIV-Related Events
- Trial closure considerations	2 Trial Closure Considerations
- Source data	3.4 Source Data
- Reporting and publication details	5.2 Use of Information and Publication
- Privacy of personal data	6.5 Privacy of Personal Data
Information regarding the following has been added:	
- A clinical status check before administration of the first dose	2.1.1.1 Flowchart for Assessments up to Week 4 in Cohort 1 (Screening and Initial Treatment Period up to Week 4)
- Questions about inclusion/exclusion criteria	6.2.2 Inclusion Criteria 6.2.3 Exclusion Criteria
- Precautions and restrictions	6.2.4 Precautions and Restrictions
- Withdrawn subjects or subjects who are lost to follow-up	6.2.5 Removal of Subjects From Therapy or Assessment 6.3.13 Prior and Concomitant Therapy
- Reporting of prohibited therapies	6.4.3 Handling of Biological Samples
- Recording of sample collection	6.6 Statistical Methods Planned and Determination of the Sample Size
- Description of statistical methods	3.1 Investigational Products
- Destruction of used and unused medication	3.2 Trial Documents 3.3 Participation Cards
- List of trial documents to be provided to the Sponsor by the site	3.5 Electronic Case Report Forms 3.6 Subject Identification Code List & Subject Screening and Enrollment Log
- Participation cards	
- Electronic case report forms (eCRFs)	3.7 Archiving
- Subject Identification Code List & Subject Screening and Enrollment Log	3.8 Protocol Amendments 3.9 Monitoring
- Trial record transfer of custody	6.2 Independent Ethics Committee/Institutional Review Board
- Administrative requirements related to protocol amendments	6.4 Subject Information and Informed Consent 6.6 Country Selection
- On-site monitoring	8 Data Quality Control/Assurance
- Reporting obligations towards the Independent Ethics Committee (IEC)/Institutional Review Board (IRB)	9 PRODUCT QUALITY COMPLAINT HANDLING
- Subject Information and Informed Consent	
- Country selection	
- The data quality control/assurance information	
- Product quality complaint handling	

	Title Page Summary 2 Flowchart 3 Overview of Trial Design 4 Introduction 5 Objectives 6.1.1 Overview of Trial 6.1.2 Discussion of Trial Design and Selection of Dose(s) in the Trial 6.2.1 Sample Size 6.2.2 Inclusion Criteria 6.2.3 Exclusion Criteria 6.2.4.2 Restrictions 6.2.5 Removal of Subjects From Therapy or Assessment 6.3.1 Identity of Investigational Product 6.3.2 Other Medication Administered in the Trial 6.3.3 Dosage and Treatment Overview Per Subject 6.3.4 Timing of Dosing 6.3.5 Individually Selected Background Regimen 6.3.9 Independent Data Monitoring Committee 6.3.12 Adherence 6.3.13.1 Disallowed Concomitant Medication 6.4.1 Timing of Assessments 6.4.2 Time Windows 6.4.7 Resistance Determinations 6.4.8.1 Sample Collection and Handling 6.4.9.2.2 Biochemistry 6.4.9.2.3 Endocrine Assessments 6.4.12 Assessment of Palatability of RPV Formulation (Other Than Tablet Formulation) 6.5 Monitoring and Safety for Specific Toxicities 6.5.5 Signs and Symptoms of Adrenal Insufficiency 6.6 Statistical Methods Planned and Determination of the Sample Size 6.6.1 Determination of Sample Size 6.6.2.2.1 Plasma viral load 6.6.2.4 Pharmacokinetic Parameter Analyses 6.6.2.5.2 Clinical Laboratory Tests 7 References 7.11 Addendum 11: Pharmacokinetic Modeling for Cohort 2 Dose Selection 5.1 Reporting
Additional section headings have been added for clarity	Throughout the protocol
Rationale: Minor corrections and administrative and textual changes were made.	

Due to a change in legal entities in Ireland, the sponsorship statement has been updated.	Title Page
Other corrections, administrative and textual changes have been made.	Summary Protocol History 1 Glossary 2.1.1.1 Flowchart for Assessments up to Week 4 in Cohort 1 (Screening and Initial Treatment Period up to Week 4) 2.1.1.2 Flowchart for Switch to Weight-adjusted Dose in Cohort 1, Part 1 Only (if applicable) 2.1.1.3 Flowchart for Assessments from Week 8 onwards in Cohort 1 (Initial Treatment Period from Week 8 onwards, Post Week 48 Treatment Extension, and Follow-up) 3.1 Cohort 1: Adolescent Subjects Aged ≥12 to <18 Years 4 Introduction 5 Objectives 6.1.1 Overview of Trial 6.1.1.1 Cohort 1: Adolescents Aged ≥12 to <18 Years 6.1.2.1 Cohort 1: Adolescents Aged ≥12 to <18 Years 6.2.1.1 Cohort 1: Adolescents Aged ≥12 to <18 Years 6.2.2 Inclusion Criteria 6.2.3 Exclusion Criteria 6.2.4.1 Precautions 6.2.5 Removal of Subjects From Therapy or Assessment 6.3.1 Identity of Investigational Product 6.3.2 Other Medication Administered in the Trial 6.3.4 Timing of Dosing 6.3.5 Individually Selected Background Regimen 6.3.6 Packaging and Labeling 6.3.10 Drug Accountability 6.3.11 Storage 6.4.1 Timing of Assessments 6.4.7 Resistance Determinations 6.4.9.2.3 Endocrine Assessments 6.4.9.2.3.1 Cohort 1: Adolescents Aged ≥12 to <18 Years 6.4.9.3.2 ECG 6.4.10 Adherence Questionnaire 6.5.1 Cutaneous Event/Rash 6.5.3 AST, ALT, and Total Bilirubin Elevation 6.5.5.1 Cohort 1: Adolescents Aged ≥12 to <18 Years 6.5.11.4 Lactic Acidosis 6.5.11.5Renal Complications 6.6 Statistical Methods Planned and Determination of the Sample Size 6.6.1.1 Cohort 1: Adolescents Aged ≥12 to <18 Years 6.6.2.2.1 Plasma viral load 6.6.2.2.1.1 Analysis 6.6.2.3 Resistance 6.6.2.4 Pharmacokinetic Parameter Analyses 6.6.2.5.2 Clinical Laboratory Tests 6.6.2.6 Diaries 6.6.2.7 Questionnaires 7.3 Addendum 3: Visit Schedule for Cutaneous Reaction/Rash Follow-up 7.12 Addendum 12: Taste Assessment Form for Children

	1.4 Reporting of AEs and HIV-Related Events 3.1 Investigational Products
TMC278 has been changed to rilpivirine or RPV	Throughout the protocol

Amendment GEN-V (Issued Date: 29-Aug-2013)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: As part of its portfolio review, Janssen Diagnostics has decided to discontinue virco®TYPE HIV-1 by end 2013 in clinical practice. In addition, Janssen Diagnostics discontinued routine use of Antivirogram® in 2012 and will cease to provide this service also for clinical trials. Therefore, for genotypic and phenotypic resistance testing in this protocol, another geno- and phenotyping assay will be implemented.

Description of Change(s)	Applicable Section(s)
Rationale: As part of its portfolio review, Janssen Diagnostics has decided to discontinue virco®TYPE HIV-1 by end 2013 in clinical practice. In addition, Janssen Diagnostics discontinued routine use of Antivirogram® in 2012 and will cease to provide this service also for clinical trials. Therefore, for genotypic and phenotypic resistance testing in this protocol, another geno- and phenotyping assay will be implemented. Any reference to virco®TYPE HIV-1 or Antivirogram® in the protocol is through this amendment being replaced by a more generic term for geno-/phenotypic testing.	
	2.1.1.1 Flowchart for Assessments up to Week 4 (Screening and Initial Treatment Period up to Week 4) 2.1.1.2 Flowchart for Switch to Weight-adjusted Dose (if applicable) 2.1.1.3 Flowchart for Assessments from Week 8 onwards (Initial Treatment Period from Week 8 onwards, Post Week 48 Treatment Extension, and Follow-up) 3 Overview of Trial Design 6.1.1 Overview of Trial 6.1.2 Discussion of Trial Design and Selection of Dose(s) in the Trial 6.2.2 Inclusion Criteria 6.2.5 Removal of Subjects From Therapy or Assessment 6.3.5 Individually Selected Background Regimen 6.4.7 Resistance Determinations 6.5.11.3 Hypersensitivity Reactions 6.6.2.3 Resistance determinations
Rationale: Update to reflect the status of the study and the results of Part 1, and addition of an Independent Data Monitoring Committee analysis for Part 1 and Part 2, at Week 12, to bring in line with the actual performed and planned analysis.	
	Summary 3 Overview of Trial Design 6.1.1 Overview of Trial 6.1.2 Discussion of Trial Design and Selection of Dose(s) in the Trial 6.6 Statistical Methods Planned and Determination of the Sample Size
Rationale: Exploratory analyses on virologic response and change in $CD4^+$ cell count were removed from the statistical methods, as the study size will not be sufficiently large to make valuable conclusions.	
	6.6.2.2.1.1 Analysis 6.6.2.2.2 Immunology

Rationale: Following the implementation of the ICH E2F guideline, the Annual Safety Report has been replaced with the Development Safety Update Report. Until 2011, the data lock of the Development Safety Update report was 23 August. From 2012 onward, the data lock was aligned with the International Birth Date of 20 May 2011 (after approval of RPV in the United States).	
	1 Glossary Part 2, 5.1 Reporting Part 2, 6.2 Independent Ethics Committee/Institutional Review Board
Rationale: Per the revised template wording, a clarification was added with regards to the reporting by the laboratory of certain laboratory data in addition to those required per protocol.	
	6.4.9.2.4 Urinalysis
Rationale: The sponsor has decided to harmonize the procedures for emergency medical questions and product complaints. Therefore, the telephone number mentioned on the title page has been removed. Appropriate information about who should be contacted regarding safety issues or questions regarding the study is provided in Section 8.1, Addendum 1, Trial Contact Persons	
Removal of the emergency phone number.	Title Page
Rationale: Timing of the completion of the adherence questionnaire in the Flowchart did not match the timing mentioned in the questionnaire itself. The assessment at Week 240 is removed from the Flowchart. It is specified that questionnaires appended in this protocol are sample questionnaires, and that sites should always use the most recently provided version of the questionnaire.	
	2.1.1.3 Flowchart for Assessments from Week 8 onwards (Initial Treatment Period from Week 8 onwards, Post Week 48 Treatment Extension, and Follow-up) 6.4.10 Adherence Questionnaire 8.7 Addendum 7: Study Adherence Questionnaire for Children and Teenagers 8.8 Addendum 8: Study Adherence Questionnaire for Caregivers
Rationale: Some administrative and textual changes were made.	
Per revised template, addition of a footnote in the Flowchart, to clarify that informed consent must be obtained prior to any study related activity.	2.1.1.1 Flowchart for Assessments up to Week 4 (Screening and Initial Treatment Period up to Week 4)
Deletion of duplicated information.	Title Pages
Minor typographic error	6.1.1 Overview of Trial
Other textual changes, to improve consistency in the document.	2.1.1.1 Flowchart for Assessments up to Week 4 (Screening and Initial Treatment Period up to Week 4) 2.1.1.3 Flowchart for Assessments from Week 8 onwards (Initial Treatment Period from Week 8 onwards, Post Week 48 Treatment Extension, and Follow-up) 6.1.1 Overview of Trial 6.2.3 Exclusion Criteria 6.4.10 Adherence Questionnaire

Amendment GEN-IV (Issued Date: 02-Feb-2012)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Based on correspondence exchange with the Food and Drug Administration (FDA), Snapshot analysis was added, as a secondary efficacy analysis. At the request of the Pediatric Committee (PDCO), the timing of the Week 12 interim analysis was changed.

Description of Change(s)	Applicable Section(s)
Rationale: Addition of snapshot analysis, as a secondary efficacy analysis, as requested by the FDA.	
Addition of Snapshot analysis.	6.6.2.2.1.1 Analysis
Rationale: At the request of the PDCO, the timing of Week 12 interim analysis changed from 'when all subjects have reached 12 weeks of treatment or discontinued earlier' to 'when all Part 1a and Part 1b subjects have reached 12 weeks of treatment or discontinued earlier'.	
Week 12 interim analysis will be performed when all Part 1 subjects have reached Week 12 or discontinued earlier.	6.1.1 Overview of Trial 6.3.9 Independent Data Monitoring Committee 6.6 Statistical Methods Planned and Determination of the Sample Size
Rationale: Changes of Protocol Amendment III were not made consistently/correctly throughout the protocol.	
Flowchart for switch to weight-adjusted dose was updated through Amendment III. However, footnote *i* was inadvertently left in while it should have been deleted.	2.1.1.2 Flowchart for Switch to Weight-adjusted Dose (if applicable)
4-week follow-up visit should take place regardless of the presence of (S)AEs if subjects withdraw early (i.e., before Week 48) or if subjects do not participate in the extension after Week 48. After Week 48, a 4-week follow-up visit is only required in case of ongoing (S)AEs at the final on-treatment visit.	Summary 2.1.1.3 Flowchart for Assessments from Week 8 onwards (Initial Treatment Period from Week 8 onwards, Post Week 48 Treatment Extension, and Follow-up) 3 Overview of Trial Design 6.1.1 Overview of Trial 6.2.5 Removal of Subjects From Therapy or Assessment
In the post Week 48 treatment extension period, the time window for study visits is +/-1 week.	6.4.2 Time Windows
Pharmacokinetic parameter analyses applicable for Part 1 should take place on Day 14 for Part 1a and on Day 28 for Part 1b.	6.6.2.4 Pharmacokinetic Parameter Analyses
Since Week 48 and Week 96 Phase III data are now available, AUC are and will be compared with these Phase III data.	6.6.2.4 Pharmacokinetic Parameter Analyses

Rationale: The name of the sponsor of the trial changed from Tibotec Pharmaceuticals to Janssen R&D Ireland because of the transition of the Johnson & Johnson Research & Development companies to a unified Janssen identity.	
The name of the sponsor of the trial changed.	Title Page Summary 6.3.1 Identity of Investigational Product 6.5.1 Cutaneous Event/Rash 8.2 Addendum 2: DAIDS Table
Rationale: Some administrative and textual changes were made.	
Administrative and textual changes	Title Page List of Abbreviations 2.1.1.1 Flowchart for Assessments up to Week 4 (Screening and Initial Treatment Period up to Week 4) 2.1.1.2 Flowchart for Switch to Weight-adjusted Dose (if applicable) 2.1.1.3 Flowchart for Assessments from Week 8 onwards (Initial Treatment Period from Week 8 onwards, Post Week 48 Treatment Extension, and Follow-up) 3 Overview of Trial Design 4 Introduction 5 Objectives 6.1.2 Discussion of Trial Design and Selection of Dose(s) in the Trial 6.2.4.1 Precautions 6.2.5 Removal of Subjects From Therapy or Assessment 6.3.3 Dosage and Treatment Overview Per Subject 6.3.13.1 Disallowed Concomitant Medication 6.4.7 Resistance Determinations 6.4.10 Adherence Questionnaire 6.5.5 Signs and Symptoms of Adrenal Insufficiency 6.5.9 Diarrhea 6.5.10 Other Toxicities 6.5.11.3 Hypersensitivity Reactions 6.6.1 Determination of Sample Size 6.6.2.2.1 Plasma viral load 6.6.2.3 Resistance determinations 6.6.2.4 Pharmacokinetic Parameter Analyses 1.4 Reporting of AEs and HIV-Related Events

PART 1. CLINICAL TRIAL PROTOCOL

1. GLOSSARY

List of Abbreviations

ABC	abacavir
ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST/SGOT	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24h}	AUC from time of administration up to 24 hours post dosing
AZT	zidovudine
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CL/F	total apparent plasma clearance at steady-state
C_{0h}	predose (trough) plasma concentration
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration between 0 hour and τ (τ = dosing interval)
CPMP	Committee for Proprietary Medicinal Products
Cl_{Cr}	creatinine clearance
$C_{ss,av}$	average steady-state plasma concentration
%CV	percentage of coefficient of variation
CV	coefficient of variation
CYP3A4	cytochrome P450, isoenzyme 3A4
d4T	stavudine
DAIDS	Division of AIDS
DBP	diastolic blood pressure
ddI	didanosine
DHEAS	dehydroepiandrosterone sulfate
DHHS	Department of Health and Human Services
DSUR	Development Safety Update Report
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EFV	efavirenz
ENF	enfuvirtide
ETR	etravirine
FDA	Food and Drug Administration
FSH	folllicle stimulating hormone
FTC	emtricitabine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase

HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV-1(2)	human immunodeficiency virus - type 1 (type 2)
HLA	Haman Leukocyte Antigen
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
IAS-USA	International Antiviral Society United State of America
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ITT	intent-to-treat
IRB	Institutional Review Board
IUD	intra-uterine device
LDL	low density lipoprotein
LH	luteinizing hormone
LOCF	last observation carried forward
LS	least square
MCH	mean corpuscular hemoglobin
M = F	missing = failure
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MTCT	mother-to-child transmission
n	number of observations
NA	not applicable
NC = F	non-completer = failure
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside/nucleotide analogue reverse transcriptase inhibitor
NVP	nevirapine
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	protease inhibitor
PK	pharmacokinetic
PMTCT	prevention of mother-to-child transmission
PoP	proof-of-principle
PR	pulse rate
PQC	product quality complaint
QA	Quality Assurance
QC	Quality Control
q.d.	quaque die; once daily
RAM	resistance-associated mutation
RBC	red blood cell
RNA	ribonucleic acid
RPV	rilpivirine
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
sdNVP	single dose of nevirapine
SJS	Stevens-Johnson Syndrome
SUSAR	suspected unexpected serious adverse reaction
3TC	lamivudine
TDF	tenofovir disoproxyl fumarate
TEN	toxic epidermal necrolysis
TLOVR	time to loss of virologic response
t_{max}	time to reach the maximum plasma concentration

TMC	Tibotec Medicinal Compound
$t_{1/2,term}$	terminal elimination half-life
ULN	upper limit of laboratory normal range
USA	United States of America
VL	viral load
WBC	white blood cell

Definition of terms

BMI	Weight in kg divided by the square of the height in meters
QTcB	QT interval corrected for heart rate using Bazzet's formula $QTc = QT \times (1000/RR)^b$ where b = 1/2
QTcF	QT interval corrected for heart rate using Fridericia's formula $QTc = QT \times (1000/RR)^b$ where b = 1/3
Study drug	the medication under investigation (RPV in this trial)
Background regimen	the 2 investigator-selected N(t)RTIs
ARV medication	all ARV medication administered in this trial, i.e., RPV and the background regimen
Virologic Response	2 consecutive measurements of <400 HIV-1 RNA copies/mL
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
Lack of response	Confirmed decrease in plasma viral load of <1.0 $\log_{10}$ at Week 12 from the baseline viral load (i.e., 2 consecutive measurements at least 2 weeks apart)
Loss of response	Two consecutive measurements of >400 HIV-1 RNA copies/mL at least 2 weeks apart after having been confirmed virologic responder

2. FLOWCHART

2.1. Cohort 1: Adolescents Aged ≥12 to <18 Years

2.1.1. Flowchart for All Assessments in Cohort 1 (Screening, Initial Treatment Period, Post Week 48 Treatment Extension, and Follow-up)

2.1.1.1. Flowchart for Assessments up to Week 4 in Cohort 1 (Screening and Initial Treatment Period up to Week 4)

Type of Visit	Screening*	Baseline	Initial Treatment Period**		
Time of Visit	W-6	D 1	W 1	W 2***	W 4***
Informed consent[bb], demographic data, medical and surgical history, concomitant diseases	#				
Inclusion/exclusion criteria	#	#			
HLA-B*5701 testing[a]	X				
Determination of plasma viral load	# *	#		#	#
Immunology	#	#		#	#
Samples for viral phenotype/genotype determinations[b,c]	#	#		#	# [d]
Hematology & biochemistry[e]	# *	# [f]	X	#	#
Electrocardiogram (ECG)[g]	X			X[h]	X[i]
Vital signs (Pulse, blood pressure [BP])	#	#		#	#
Physical examination	#	#	X	# [j]	# [k]
Height/weight[l]	#	#	X[m]	# [m]	# [m]
Check occurrence of first menses[n]	X	X	X	X	X
Evaluation of pubertal development (Tanner scale)		#			
Contraceptive counselling[o]	X				
Pregnancy test[p]	#	#			#
Urinalysis	#	#	X	#	#
Sampling for pharmacokinetics[q]				X[r]	# [s]
Cortisol (and adrenocorticotropic hormone [ACTH] stimulation testing if applicable)[t]		X			X
Endocrine assessments[u]		X			
Cortisol, 17-hydroxyprogesterone, aldosterone assessments, and ACTH stimulation testing[v]		X			
Treatment adherence counseling and checking of adherence[w]	X	X	X	X	X
Study Adherence Questionnaire for Children and Teenagers and/or Carers[x]			X	X	#

Type of Visit	Screening*	Baseline	Initial Treatment Period**		
Time of Visit	W-6	D 1	W 1	W 2***	W 4***
Evaluation for depression[y]		X		X	X
Dispensation of antiretroviral (ARV) medication		#	X	#	#
Drug accountability				#	#
Completion of diary[z]		X	X	X	X
Concomitant therapy[aa]	#	#	X	#	#
Observe/Interview for adverse events (AEs), including HIV-related events[aa]		#	X	#	#

* During the screening period it is allowed to assess the viral load and $CD4^+$ cell count before continuing with the other screening assessments. After obtaining informed consent, samples will be taken for determination of plasma viral load and $CD4^+$ cell count. If plasma viral load results meet the inclusion criteria and the investigator considers initiation of ART appropriate (taking into account current treatment guidelines, including $CD4^+$ cell count and the subject's clinical situation), the subject 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 subject 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 assessment, if these were assessed separately before continuing with the other screening assessments), but in case of unforeseeable circumstances, this period can be prolonged by 2 weeks maximum.

** Unscheduled visits may be performed for safety/tolerability reasons and for confirmation of plasma viral load results (see Section 6.4.1).

*** If the short-term Part 1 results show a safety concern, that potentially could be avoided by lower exposure to RPV, as deemed by the IDMC, subjects up to a certain body weight (determined based on the intensive pharmacokinetic results) will be switched to a lower, weight-adjusted dose of RPV. Please refer to the flowchart in Section 2.1.1.2 for further details. If the Week 2 results are not deemed satisfactory by the IDMC, all subjects will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to a locally available ARV regimen, and the trial will be stopped. For more details on the trial design and stopping rules, please refer to Section 6.1.1.

[a] HLA-B*5701 testing is only required for subjects for whom the investigator considers ABC in the background regimen and is not required for subjects with prior documented HLA-B*5701 negative results. The test involves a cheek swab. No eating or drinking is allowed for 30 minutes before the swab. In those subjects where HLA-B*5701 is positive, ABC cannot be administered, but instead, the investigator should select another N(t)RTI in the background regimen.

[b] Samples collected at screening will be tested in real time for the determination of the HIV-1 genotype. These HIV-1 genotyping results will be provided to the investigator as soon as they are available. Samples collected at baseline and at the first visit after confirmed loss of response (see Section 6.2.5) will be tested for the determination of the HIV-1 genotype, as long as the viral load is sufficiently high to allow HIV-1 genotyping.
Phenotyping will be done at baseline. Samples will be analyzed as long as the viral load is sufficiently high to allow phenotyping. Samples collected at other intervals may be selected for the determination of HIV-1 genotype and/or phenotype by the Protocol Virologist based on plasma viral load.

[c] In case Cohort 1 is stopped after Part 1, a sample will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ARV regimen. When determination of HIV-1 genotype on this sample is not possible due to a too low viral load, the new ARV regimen will be based on the screening HIV-1 genotyping result.

[d] Samples for viral phenotype/genotype will only be taken if the plasma viral load at the previous visit was >50 HIV-1 RNA copies/mL. If at a certain visit the plasma viral load, after having been < 50 HIV-1 RNA copies/mL at a previous visit, has increased to >50 HIV-1 RNA copies/mL, samples for viral phenotype/genotype should be taken at an unscheduled visit.

[e] Sample should be taken fasted (overnight).

Footnotes continue on the next page

[f] A hepatitis A, B, and C test will be performed at baseline, and whenever clinically relevant, extra tests can be done at other visits. The hepatitis C test will be a hepatitis C virus (HCV)-antibody test. Only in case the $CD4^+$ cell count at screening was <100 cells/mm^3 or in case the HCV-antibody test at baseline was positive, a qualitative HCV RNA sample should be drawn at Week 1.

[g] Whenever possible, the ECG should be taken at expected C_{max} (i.e., 4 hours after intake of RPV). Additional ECGs must be performed in case of start of certain concomitant medication (see Section 6.3.13.1).

[h] For Part 1a subjects only.

[i] For Part 1b and Part 2 subjects only.

[j] Only skin examination.

[k] A brief physical examination only.

[l] Growth will be followed using the standardized charts (see Section 6.4.9.4).

[m] Height does not need to be measured.

[n] At screening, it will be assessed whether girls already have had their first menses. As part of the evaluation of pubertal development, for girls who have not yet had their first menses at screening, it will be checked at every visit whether they have had their first menses and the date of first menses will be recorded.

[o] It is the investigator's responsibility to ensure that the subjects receive appropriate counseling about precautions to reduce the risk of transmitting HIV and birth control methods (see Section 6.2.4.1). Girls having their first menses during the trial should receive counseling again.

[p] Serum test at screening and urine test at other visits, for girls of childbearing potential.

[q] A pharmacokinetic sample will be taken at any time during the visit. The date and time of sampling and the date and time of the RPV intake prior to that sample should be recorded on the electronic Case Report Form (eCRF). Where possible (i.e., if that RPV intake occurs during the visit), at least on one occasion, the sample will be taken just prior to RPV intake.

[r] For Part 1a subjects only: intensive pharmacokinetic sampling took place at the Week 2 visit. See Section 2.1.2 for details.
For Part 1b and Part 2 subjects only: sparse pharmacokinetic sampling will take place at the Week 2 visit.

[s] For Part 1b subjects only: intensive pharmacokinetic sampling will take place at the Week 4 visit. See Section 2.1.2 for details.

[t] Basal cortisol will be measured in the morning at the indicated visits, between 7h30 and 9h30. If at any visit, as of the baseline visit, basal cortisol value is <248 nmol/L (9 µg/dL) a retest will be done at the subsequent visit or at least within the next 8 weeks. If 2 consecutive basal cortisol values are <248 nmol/L (9 µg/dL), an ACTH stimulation test will be done at the next scheduled visit with measurements of cortisol, 17-hydroxyprogesterone, and aldosterone before (T_0), 30 (T_{30}) and 60 (T_{60}) minutes after ACTH stimulation (see Section 6.4.9.2.3). In case of clinical signs or symptoms or laboratory abnormalities (other than cortisol) indicative of adrenal insufficiency (see Section 6.5.5), an ACTH stimulation test should be done as soon as possible during an unscheduled visit. If an unscheduled ACTH stimulation test is performed at a visit with a scheduled basal cortisol assessment, only one sample needs to be collected for the determination of basal (T_0) cortisol.

[u] Assessment of follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, androstenedione, testosterone, dehydroepiandrosterone sulfate (DHEAS) in conjunction with the basal (T_0) cortisol assessment.

[v] ACTH stimulation test including measurements of cortisol, 17-hydroxyprogesterone and aldosterone, measured before (T_0), 30 (T_{30}) and 60 (T_{60}) minutes after ACTH stimulation, at baseline (see Section 6.4.9.2.3). If the ACTH stimulation test is abnormal (i.e., all cortisol values [before and after ACTH stimulation] are <500 nmol/L [18.1 µg/dL]), a retest needs to be performed at the next scheduled visit. In case of withdrawal due to pregnancy, no ACTH stimulation test needs to be performed, but basal assessments need to be performed.

[w] Treatment adherence counseling should be performed at screening and baseline; treatment adherence should be checked and counseling repeated at every visit thereafter (see Section 6.3.12).

[x] Questionnaires will only be administered if a certified translation is available in the local language.

[y] Evaluation should be done according to local standard of care at the site (see Section 6.4.11 for details).

[z] For Part 1a and Part 1b subjects only: subjects, their parent(s), or caregiver(s) will have to complete a diary documenting the intake of RPV from the start of treatment until the day of intensive pharmacokinetic sampling.

[aa] Adverse events (including HIV-related events and the occurrence of AIDS-defining illnesses) and the intake of concomitant medication will be monitored throughout the trial from signing of the informed consent form (ICF) onwards until the last trial-related activity.

[bb] Informed consent must be obtained prior to any trial-related activity.

2.1.1.2. Flowchart for Switch to Weight-adjusted Dose in Cohort 1, Part 1 Only (If Applicable)

Note: The following flowchart was also applicable for subjects in Part 1a in case of switch to weight-adjusted dose. However, after review of Part 1a Week 2 data the IDMC did not warrant the need for a switch to weight-adjusted dose. Recruitment for Part 1a has been closed in the meantime.

Type of Visit	Initial Treatment Period*	
Time of Visit	Dose Switch Visit**	Post Switch Visit***
Determination of plasma viral load		#
Immunology		#
Samples for viral phenotype/genotype determinations[a,b]		#
Hematology & biochemistry[c]		#
Electrocardiogram (ECG)[d]		X
Vital signs (Pulse, blood pressure [BP])		#
Physical examination		#[e]
Height/weight[f]		#[g]
Check occurrence of first menses[h]		X
Urinalysis		#
Sampling for pharmacokinetics		X[j]
Treatment adherence counseling and checking of adherence	X	X
Study Adherence Questionnaire for Children and Teenagers, if applicable[k]		X
Evaluation for depression[l]		X
Dispensation of antiretroviral (ARV) medication	X	#
Drug accountability		#
Completion of diary[m]		X
Concomitant therapy[n]	#	#
Observe/Interview for adverse events (AEs), including HIV-related events[n]	#	#

* Unscheduled visits may be performed for safety/tolerability reasons, for confirmation of plasma viral load results, and for the dose switch visit and/or post switch visit (see Section 6.4.1).

** As soon as the recommended pediatric dose is communicated, subjects from Part 1 will have to attend a dose switch visit (unscheduled visit) in order to be provided with RPV at the recommended weight-adjusted dose, if applicable. If the dose switch visit is done within 1 week of the next scheduled visit as indicated in the flowchart, this next planned visit can be cancelled but assessments of that visit will have to be performed at the dose switch visit.

*** A re-evaluation of subjects who have been treated with the weight-adjusted dose for 4 weeks (+/-1 week) will be done (unscheduled visit). If the post switch visit is done within 1 week of the next planned visit as indicated in the flowchart, this next planned visit can be cancelled but assessments of that visit that are not planned at the post switch visit will have to be added to the planned assessments at the post switch visit.

a Samples collected at the first visit after confirmed loss of response (see Section 6.2.5) will be tested for the determination of the HIV-1 genotype, as long as the viral load is sufficiently high to allow HIV-1 genotyping.
Samples collected at other intervals may be selected for determination of the HIV-1 genotype and/or phenotype by the Protocol Virologist based on plasma viral load.

b In case the Cohort 1 is stopped after Part 1, a sample will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ARV regimen. When determination of HIV-1 genotype on this sample is not possible due to a too low viral load, the new ARV regimen will be based on the screening HIV-1 genotype result.

c Sample should be taken fasted (overnight).

Footnotes continue on the next page

[d] Whenever possible, the ECG should be taken at expected C_{max} (i.e., 4 hours after intake of RPV). Additional ECGs must be performed in case of start of certain concomitant medication (see Section 6.3.13.1).

[e] Only skin examination.

[f] Growth will be followed using the standardized charts (see Section 6.4.9.4).

[g] Height does not need to be measured.

[h] As part of the evaluation of pubertal development, for girls who have not yet had their first menses at screening, it will be checked at every visit whether they have had their first menses and the date of first menses will be noted.

[j] For Part 1a subjects only: intensive pharmacokinetic sampling was to take place at the post switch visit (at least 2 weeks after the dose switch visit). See Section 2.1.2 for details.
For Part 1b subjects only: intensive pharmacokinetic sampling will take place at the post switch visit (4 weeks [+/-1 week] after the dose switch visit). See Section 2.1.2 for details.

[k] Questionnaires will only be administered if a certified translation is available in the local language.

[l] Evaluation should be done according to local standard of care at the site (see Section 6.4.11 for details).

[m] For Part 1a and Part 1b subjects only: subjects, their parent(s), or caregiver(s), will have to complete a diary documenting the intake of RPV from the start of treatment with the weight-adjusted dose until the day of intensive pharmacokinetic sampling.

[n] Adverse events (including HIV-related events and the occurrence of AIDS-defining illnesses) and the intake of concomitant medication will be monitored throughout the trial from signing of the informed consent form (ICF) onwards until the last trial-related activity.

2.1.1.3. Flowchart for Assessments From Week 8 Onwards in Cohort 1 (Initial Treatment Period From Week 8 Onwards, Post Week 48 Treatment Extension, and Follow-up)

Type of Visit	Initial Treatment Period*						Final/ Withdrawal Visit**	Post Week 48 Treatment Extension*		Final/ Post Week 48 Withdrawal Visit***	Post-treatment Follow-up Period****
Time of Visit	W 8	W 12	W 16	W 24	W 32	W 40	W 48	Every 3 Months	Every 6 Months	W 240	4 Weeks After Final/Withdrawal Visit
Informed consent[a]							X				
Determination of plasma viral load	X	X	X	X	X	X	X	X	X	X	X
Immunology		X		X	X	X	X	X	X	X	
Samples for viral phenotype/genotype determinations[b]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X	X	X
Hematology & Biochemistry[d,e]	X	X	X	X	X	X	X		X	X	X
Electrocardiogram (ECG)[f]		X		X			X			X	
Vital signs (Pulse, blood pressure [BP])	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[g]	X	X[g]	X	X[g]	X[g]	X	X[g]	X	X	X[g]
Height/weight[h]	X	X[i]	X	X	X	X	X		X	X	X
Check occurrence of first menses[j]	X	X	X	X	X	X	X	X	X	X	X
Evaluation of pubertal development (Tanner scale)		X		X		X	X		X	X	X
Pregnancy test[k]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
Sampling for pharmacokinetics[l]	X	X		X			X			X	
Cortisol (and adrenocorticotropic hormone [ACTH] stimulation testing if applicable)[m]		X		X			X			X	X
Endocrine assessments[n]		X		X			X			X	
Cortisol, 17-hydroxyprogesterone, aldosterone assessments, and ACTH stimulation testing[o]		X		X			X			X	
Treatment adherence counseling and checking of adherence	X	X	X	X	X	X	X	X	X	X	X
Study Adherence Questionnaire for Children and Teenagers and/or Carers[p]	X	X	X	X	X	X	X				
Evaluation for depression[q]	X	X	X	X	X	X	X	X	X	X	X
Dispensation of antiretroviral (ARV) medication	X	X	X	X	X	X	X[r]	X	X		
Drug accountability	X	X	X	X	X	X	X	X	X	X	
Concomitant therapy[s]	X	X	X	X	X	X	X	X	X	X	X

Type of Visit	Initial Treatment Period*						Final/ Withdrawal Visit**	Post Week 48 Treatment Extension*		Final/ Post Week 48 Withdrawal Visit***	Post-treatment Follow-up Period****
Time of Visit	W 8	W 12	W 16	W 24	W 32	W 40	W 48	Every 3 Months	Every 6 Months	W 240	4 Weeks After Final/Withdrawal Visit
Observe/interview for adverse events (AEs), including HIV-related events[s]	X	X	X	X	X	X	X	X	X	X	X

* Unscheduled visits may be performed for safety/tolerability reasons and for confirmation of plasma viral load results (see Section 6.4.1).

** For subjects who discontinue the trial before Week 48, this is the Withdrawal visit; otherwise this is the Final visit.

*** For subjects who discontinue the trial after Week 48 but before Week 240, this the Withdrawal visit; otherwise this is the Final visit.

**** In the initial treatment period, the 4-week Follow-up visit is only performed for subjects who withdraw early from the trial (i.e., before Week 48) (unless consent is withdrawn) or who do not participate in the extension after Week 48. In the extension period the 4-week Follow-up visit is only performed if there is an ongoing (S)AE at the last on-treatment visit.

[a] Informed consent to the post Week 48 treatment extension must be given prior to the start of this treatment extension.

[b] Samples collected at the first visit after confirmed loss of response (see Section 6.2.5), at the Week 48 visit, and at the Final/Withdrawal visit will be tested for the determination of the HIV-1 genotype, as long as the viral load is sufficiently high to allow HIV-1 genotyping.
Phenotype will be done at the Week 48 visit and at the Final/Withdrawal visit. Samples will be analyzed as long as the viral load is sufficiently high to allow phenotyping.
Samples collected at other intervals may be selected for determination of the HIV-1 genotype and/or phenotype by the Protocol Virologist based on plasma viral load.

[c] Samples for viral phenotype/genotype will only be taken if the plasma viral load at the previous visit was >50 HIV-1 RNA copies/mL. If at a certain visit the plasma viral load, after having been <50 HIV-1 RNA copies/mL at a previous visit, has increased to >50 HIV-1 RNA copies/mL, samples for viral phenotype/genotype should be taken at an unscheduled visit.

[d] Sample should be taken fasted (overnight).

[e] Tests can be performed whenever clinically relevant. The hepatitis C test will be a hepatitis C virus (HCV)-antibody test.

[f] Whenever possible, the ECG should be taken at expected C_{max} (i.e., 4 hours after intake of RPV). Additional ECGs must be performed in case of start of certain concomitant medication (see Section 6.3.13.1).

[g] A brief physical examination only.

[h] Growth will be followed using the standardized charts (see Section 6.4.9.4).

[i] Height does not need to be measured.

[j] As part of the evaluation of pubertal development, for girls who have not yet had their first menses at screening, it will be checked at every visit whether they have had their first menses and the date of first menses will be noted.

[k] Urine test for girls of childbearing potential.

[l] A pharmacokinetic sample will be taken at any time during the visit. The date and time of sampling and the date and time of the RPV intake prior to that sample should be recorded on the electronic Case Report Form (eCRF). Where possible (i.e., if that RPV intake occurs during the visit), at least on one occasion, the sample will be taken just prior to RPV intake.

[m] Basal cortisol will be measured in the morning at the indicated visits, between 7h30 and 9h30. If at any visit, as of the baseline visit, basal cortisol value is <248 nmol/L (9 µg/dL) a retest will be done at the subsequent visit or at least within the next 8 weeks. If 2 consecutive basal cortisol values are <248 nmol/L (9 µg/dL), an ACTH stimulation test will be done at the next scheduled visit with measurements of cortisol, 17-hydroxyprogesterone, and aldosterone before (T_0), 30 (T_{30}) and 60 (T_{60}) minutes after ACTH stimulation (see Section 6.4.9.2.3). In case of clinical signs or symptoms or laboratory abnormalities (other than cortisol) indicative of adrenal insufficiency (see Section 6.5.5),

an ACTH stimulation test should be done as soon as possible during an unscheduled visit. If an unscheduled ACTH stimulation test is performed at a visit with a scheduled basal (T_0) cortisol assessment, only one sample needs to be collected for the determination of basal cortisol.

[n] Assessment of follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, androstenedione, testosterone, dehydroepiandrosterone sulfate (DHEAS) in conjunction with the basal (T_0) cortisol assessment.

[o] ACTH stimulation test including measurements of cortisol, 17-hydroxyprogesterone and aldosterone, measured before (T_0), 30 (T_{30}) and 60 (T_{60}) minutes after ACTH stimulation, needs to be performed at Week 48 (see Section 6.4.9.2.3). If the ACTH stimulation test is abnormal (i.e., all cortisol values [before and after ACTH stimulation] are <500 nmol/L [18.1 µg/dL]), a retest needs to be performed at the next scheduled visit. At Week 12 and 24, no ACTH stimulation test needs to be performed, only basal assessments of cortisol, 17-hydroxyprogesterone and aldosterone. In case of withdrawal due to pregnancy, no ACTH stimulation test needs to be performed, but basal assessments need to be performed.

[p] Questionnaires will only be administered if a certified translation is available in the local language.

[q] Evaluation should be done according to local standard of care at the site (see Section 6.4.11 for details).

[r] Only for subjects who enter the post Week 48 treatment extension.

[s] Adverse events (including HIV-related events and the occurrence of AIDS-defining illnesses) and the intake of concomitant medication will be monitored throughout the trial from signing of the informed consent form (ICF) onwards until the last trial-related activity.

2.1.2. Flowchart for Intensive Pharmacokinetic Sampling in Cohort 1, Part 1 Only

Note: For Part 1a subjects, intensive pharmacokinetic sampling was to take place after at least 2 weeks of treatment with rilpivirine (RPV) 25 mg q.d. or a weight-adjusted dose q.d. For Part 1b subjects, intensive pharmacokinetic sampling will take place after 4 weeks (+/-1 week) of treatment with RPV 25 mg q.d. or a weight-adjusted dose q.d.

Time	Blood Sample[a]	ECG, Pulse Rate (PR), BP	Other
			Admission to unit
Predose	X[b]	X[c,d]	Standardized breakfast in unit
0 h			Intake RPV 25 mg
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[e]

[a] At each time point, 4 mL of blood should be collected (total volume of blood drawn during the 24-hour period is 32 mL).

[b] Within 1 hour before dosing.

[c] Within 2 hours before dosing.

[d] ECG and vital signs measurements should be performed preferably before blood sampling.

[e] In case it is not feasible for subjects to stay overnight, the subject can be discharged after the 12-hour sample. In this case, the subject should return to the unit for the 24-hour sample.

2.2. Cohort 2: Children Aged ≥6 to <12 Years

2.2.1. Flowchart for all Assessments in Cohort 2 (Screening, Initial Treatment Period, Post Week 48 Treatment Extension, and Follow-up)

2.2.1.1. Flowchart for Assessments up to Week 4 in Cohort 2 (Screening and Initial Treatment Period up to Week 4)

Type of Visit	Screening*	Baseline	Initial Treatment Period**		
Time of Visit[aa]	W -6	D 1	W 1	W 2***,†,††	W 4***
Informed consent[a], demographic data, medical and surgical history, concomitant diseases	#				
Check clinical status[b]		X			
Inclusion/exclusion criteria	#	X			
HLA-B*5701 testing[c]	X				
Determination of plasma viral load[d]	# *	#		#	#
Immunology	# *	#		#	#
Samples for viral phenotype/genotype determinations[e]	#	X			X
PBMC sample[z]	X				
Hematology & biochemistry[f,g]	#	#	X	#	#
Electrocardiogram (ECG)[h]	X			X	
Vital signs (Pulse, blood pressure [BP])	#	#	X	#	#
Physical examination	#	#	X	# [i]	# [j]
Height/weight[k]	#	#	X[l]	# [l]	# [l]
Check occurrence of first menses[m]	X	X	X	X	X
Evaluation of pubertal development (Tanner scale)		#			
Contraceptive counselling[n]	X				
Pregnancy test[o]	#	#			#
Urinalysis	#	#		#	
Sampling for pharmacokinetics[d]				X[††,p]	# [q]
Endocrine assessments[r]		X			
ACTH stimulation testing (cortisol, 17-hydroxyprogesterone assessments)[s]	Reflex Test				
Treatment adherence counseling and checking of adherence[t]	X	X	X	X	X
Study Adherence Questionnaire for Children and Teenagers and/or Carers[u]			X	X	#

Type of visit	Screening*	Baseline	Initial Treatment period**		
Time of Visit	W-6	D 1	W 1	W 2***,†,††	W 4***
Palatability assessment[v]		X			X
Evaluation of depression[w]		X		X	X
Dispensation of antiretroviral (ARV) medication		#			#
Drug accountability			X	#	#
Completion of diary[x]		X	X	X	
Concomitant therapy[y]	#	#	X	#	#
Observe/Interview for AEs, including HIV-related events[y]		#	X	#	#

* During the screening period it is allowed to assess the viral load and $CD4^+$ cell count before continuing with the other screening assessments. In such case, after obtaining informed consent, samples will be taken for determination of plasma viral load and $CD4^+$ cell count. If plasma viral load results meet the inclusion criteria and the investigator considers initiation of ART appropriate (taking into account current treatment guidelines, including $CD4^+$ cell count and the subject's clinical situation), the subject 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 subject 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 assessment, if these were assessed separately before continuing with the other screening assessments), but in case of unforeseeable circumstances, the screening period can be prolonged by 2 weeks resulting in a maximum screening period duration of 8 weeks.

** Unscheduled visits may be performed for safety/tolerability reasons, for reflex ACTH stimulation test in case basal cortisol is <248 nmol/L on initial and repeat testing, and for confirmation of plasma viral load results (see Section 6.4.1).

*** If the intensive PK results show a safety concern that potentially could be addressed by lower exposure to RPV, subjects will be switched to a lower dose. Please refer to the flowchart in Section 2.2.1.2 for further details. If the results after at least 4 weeks of treatment are not deemed satisfactory, all subjects will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to local standard of care, and Cohort 2 will be stopped. For more details on the trial design and dose evaluation criteria, please refer to Section 6.1.1.2 and Section 6.1.1.2.1, respectively.

† The Week 2 visit should only be scheduled for subjects with body weight of <25 kg at baseline.

†† Subjects with body weight of <25 kg or their parent(s)/caregiver(s) should be contacted via telephone or email to assess adherence (to study drug and other ARVs) and to reinforce trial instructions every day for 3 days prior to the intensive pharmacokinetic visit. If potential AEs are detected during these telephone/email contacts then the subject will be required to have an additional visit at the clinic and evaluations done as specified in Section 6.5. If the subject has missed a dose of RPV within 10 days prior to the intensive pharmacokinetic visit, the visit should be rescheduled to allow for steady-state of RPV to be reached.

a Informed consent must be obtained prior to any trial-related activity.

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

c HLA-B*5701 testing is only required for subjects for whom the investigator considers ABC in the background regimen and is not required for subjects with prior documented HLA-B*5701 negative results. The test involves a cheek swab. No eating or drinking is allowed for 30 minutes before the swab. In those subjects where HLA-B*5701 is positive, ABC cannot be administered, but instead, the investigator should select another N(t)RTI in the background regimen.

d In case of suspected virologic failure (unconfirmed loss/lack of response, see Section 1) a sample for confirmation of plasma viral load and pharmacokinetics should be taken at an unscheduled visit (see Section 6.4.1).

Footnotes continue on the next page

[e] Samples collected at screening will be tested in real time for the determination of the HIV-1 genotype. Samples collected at baseline, at virologic failure (see Section 6.2.5), at Week 48, and at the Final/Withdrawal visit will be tested for the determination of the HIV-1 genotype and phenotype, as long as the viral load is sufficiently high. Samples collected at other intervals may be selected for the determination of HIV-1 genotype and phenotype by the Protocol Virologist based on plasma viral load.

[f] Sample should be taken fasted (overnight).

[g] A hepatitis A, B, and C test will be performed at baseline, and whenever clinically relevant, extra tests can be done at other visits. The hepatitis C test will be a HCV-antibody test. Only in case the $CD4^+$ cell count at screening was <100 cells/mm^3 or in case the HCV-antibody test at baseline was positive, a qualitative HCV RNA sample should be drawn at Week 1.

[h] Whenever possible, the ECG should be taken at expected C_{max} (i.e., 4 hours after intake of RPV).

[i] Only skin examination.

[j] A brief physical examination only.

[k] Growth will be followed using the standardized charts (see Section 6.4.9.4).

[l] Height does not need to be measured.

[m] At screening, it will be assessed whether girls already have had their first menses. As part of the evaluation of pubertal development, for girls who have not yet had their first menses at screening, it will be checked at every visit whether they have had their first menses and the date of first menses will be recorded.

[n] It is the investigator's responsibility to ensure that the subjects receive appropriate counseling about precautions to reduce the risk of transmitting HIV and birth control methods (see Section 6.2.4.1). Girls having their first menses during the trial should receive counseling again.

[o] Serum test at screening and urine test at other visits, for girls of childbearing potential.

[p] Intensive pharmacokinetic sampling will take place at the Week 2 visit (Day 14-18). See Section 2.2.2 for details. Intensive pharmacokinetic sampling will only take place in subjects with a body weight of <25 kg

[q] A pharmacokinetic sample will be taken at any time during the visit. The date and time of sampling and the date and time of the RPV intake prior to that sample should be recorded on the eCRF. Where possible (i.e., if RPV intake occurs during the visit), at least on one occasion, the sample will be taken just prior to RPV intake.

[r] Assessment of FSH, LH, androstenedione, testosterone, DHEAS, in conjunction with basal cortisol and 17-hydroxyprogesterone.

[s] **As of Amendment 10** this ACTH stimulation test is not scheduled at baseline, but needs to be performed in case of confirmed abnormally low cortisol (<248 nmol/L [9 µg/dL]) or signs or symptoms of adrenal insufficiency (see Section 6.4.9.2.3.2).

[t] Treatment adherence counseling should be performed at screening and baseline; treatment adherence should be checked and counseling repeated at every visit thereafter (see Section 6.3.12).

[u] Questionnaires will only be administered if a certified translation is available in the local language.

[v] Assessment should only be done if a formulation other than the adult tablet formulation is being used.

[w] Evaluation should be done according to local standard of care at the site (see Section 6.4.11 for details).

[x] For subjects undergoing intensive PK sampling only. Subjects, their parent(s), or caregiver(s) will have to complete a diary documenting the intake of RPV from the start of treatment until the day of intensive pharmacokinetic sampling.

[y] AEs (including HIV-related events and the occurrence of AIDS-defining illnesses) and the intake of concomitant medication will be monitored throughout the trial from signing of the ICF onwards until the last trial-related activity.

[z] A peripheral blood mononuclear cell (PBMC) sample will be taken to retrospectively characterize archived viral resistance.

[aa] All study visits should be scheduled relative to the baseline visit date (eg, Day 1 + 7 days for Week 1) ± the allowed time window.

2.2.1.2. Flowchart for Switch to Adjusted Dose in Cohort 2

Note: As of Amendment 10 the following flowchart is applicable for subjects with a body weight of <25 kg as determined at baseline. 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). Dose change is not allowed between baseline (when weight is defined) and Week 2 (start of intensive PK sampling).

Type of Visit	Initial Treatment Period*		
Time of Visit	Dose Switch Visit**	2-weeks Post Switch Visit (After at Least 2 Weeks of Treatment With the Adjusted Dose)***	4-weeks Post Switch Visit (After at Least 4 weeks of Treatment With the Adjusted Dose)***
Determination of plasma viral load		#	X
Immunology		#	X
Samples for viral phenotype/genotype determinations[a]			X
Hematology & biochemistry[b]		#	X
ECG[c]		X	
Vital signs (Pulse, BP)		#	X
Physical examination		#[d]	X[e]
Height/weight[f]		#[g]	X[g]
Check occurrence of first menses[h]		X	X
Urinalysis		#	
Sampling for pharmacokinetics		X[i]	X[j]
Treatment adherence counseling and checking of adherence	X	X	X
Study Adherence Questionnaire for Children and Teenagers, if applicable[k]			X
Evaluation for depression[l]			X
Palatability assessment			X
Dispensation of ARV medication	X	#	X
Drug accountability		#	X
Completion of diary[m]		X	
Concomitant therapy[n]	#	#	X
Observe/Interview for AEs, including HIV-related events[n]	#	#	X

* Unscheduled visits may be performed for safety/tolerability reasons, for confirmation of plasma viral load results, and for the dose switch visit and/or post switch visits (see Section 6.4.1).

** As soon as the recommended pediatric dose is communicated, subjects with a body weight of <25 kg will have to attend a dose switch visit (unscheduled visit) in order to be provided with RPV at the recommended adjusted dose, if applicable. If the dose switch visit is done within 1 week of the next scheduled visit as indicated in the flowchart, this next planned visit can be cancelled but assessments of that visit will have to be performed at the dose switch visit.

*** A re-evaluation of subjects who have been treated with the adjusted dose for at least 2 weeks (between 14 and 18 days) and at least 4 weeks will be done (captured as unscheduled visits in the eCRF). If the post switch visits are done within 1 week of the next planned visit as indicated in the flowchart (see Section 2.2.1.3), this next planned visit can be cancelled but assessments of that visit that are not planned at the post switch visit will have to be added to the planned assessments at the post switch visit.

Footnotes continue on the next page

[a] Samples collected at baseline, at virologic failure (see Section 6.2.5), Week 48 and at the Final/Withdrawal visit will be tested for the determination of the HIV-1 genotype and phenotype, as long as the viral load is sufficiently high. Samples collected at other intervals may be selected for the determination of HIV-1 genotype and phenotype by the Protocol Virologist based on plasma viral load.

[b] Sample should be taken fasted (overnight).

[c] Whenever possible, the ECG should be taken at expected C_{max} (i.e., 4 hours after intake of RPV).

[d] Only skin examination.

[e] A brief physical examination only.

[f] Growth will be followed using the standardized charts (see Section 6.4.9.4).

[g] Height does not need to be measured.

[h] As part of the evaluation of pubertal development, for girls who have not yet had their first menses at screening, it will be checked at every visit whether they have had their first menses and the date of first menses will be noted.

[i] Intensive pharmacokinetic sampling will take place at the 2-weeks Post Switch visit i.e., between 14 and 18 days after the Dose Switch visit. See Section 2.2.2 for details.

[j] A pharmacokinetic sample will be taken at any time during the visit. The date and time of sampling and the date and time of the RPV intake prior to that sample should be recorded on the eCRF.

[k] Questionnaires will only be administered if a certified translation is available in the local language.

[l] Evaluation should be done according to local standard of care at the site (see Section 6.4.11 for details).

[m] For subjects undergoing intensive PK sampling only: subjects, their parent(s), or caregiver(s), will have to complete a diary documenting the intake of RPV from the start of treatment with the adjusted dose until the day of intensive pharmacokinetic sampling.

[n] AEs (including HIV-related events and the occurrence of AIDS-defining illnesses) and the intake of concomitant medication will be monitored throughout the trial from signing of the informed consent form (ICF) onwards until the last trial-related activity.

2.2.1.3. Flowchart for Assessments From Week 8 Onwards in Cohort 2 (Initial Treatment Period From Week 8 Onwards, and Follow-up)

Type of Visit	Initial Treatment Period*							Post Week 48 Treatment Extension*		Post-treatment Follow-up Period****
Time of Visit[u]	W 8	W 12	W 16	W 24	W 32	W 40	W 48**/Final Visit*	Every 3 Months	Every 6 Months	4 weeks After Final/Withdrawal Visit
Determination of plasma viral load[a]	X	X	X	X	X	X	X	X	X	X
Immunology	X	X	X	X	X	X	X	X	X	
Samples for viral phenotype/genotype determinations[b]	X	X	X	X	X	X	X	X	X	X
PBMC sample[t]							X[v]			
Hematology & Biochemistry[c]	X	X	X	X	X	X	X		X	X[d]
ECG[e]		X		X			X[f]			
Vital signs (Pulse, BP)	X	X	X	X	X	X	X	X	X	X
Physical examination	X[g]	X	X[g]	X	X[g]	X[g]	X	X[g]	X	X[g]
Height/weight[h]	X	X[i]	X	X	X	X	X		X	X
Check occurrence of first menses[j]	X	X	X	X	X	X	X	X	X	
Evaluation of pubertal development (Tanner scale)		X		X		X	X		X	
Pregnancy test[k]	X	X	X	X	X	X	X	X	X	
Urinalysis		X		X			X[f]		X	
Sampling for pharmacokinetics[a,l]	X	X		X			X[v]			
Endocrine assessments[n]				X			X[f, v]			
ACTH stimulation testing (Cortisol, 17-hydroxyprogesterone assessments)[o]	Reflex Test									
Treatment adherence counseling and checking of adherence	X	X	X	X	X	X	X	X	X	
Study Adherence Questionnaire for Children and Teenagers and/or Carers[p]	X	X	X	X	X	X	X[v]			
Evaluation for depression[q]	X	X	X	X	X	X	X	X	X	X
Dispensation of ARV medication	X	X	X	X	X	X		X	X	
Drug accountability	X	X	X	X	X	X	X	X	X	
Concomitant therapy[s]	X	X	X	X	X	X	X	X	X	X
Observe/interview for AEs, including HIV-related events[s]	X	X	X	X	X	X	X	X	X	X

* **For subjects enrolling as of Amendment 10**, the post Week 48 treatment extension has been removed. Subjects may continue treatment (i.e., RPV + 2 N[t]RTIs) in the roll-over study TMC278IFD3004 or switch to locally available RPV (once commercially available AND reimbursed, OR accessible through another source [e.g. access program or government program]), or other locally available RPV-based regimens. Subjects from Cohort 2 already in the post Week 48 treatment extension period will have to stop participation in C213 and will have the same options for continuing treatment. Visits will continue every 3 and 6 months until roll over to study TMC278IFD3004 is completed. Subjects should transition to TMC278IFD3004 at the next planned Post Week 48 treatment extension visit after Amendment 10 is approved. Any retest, of abnormal laboratory results or plasma viral load/resistance testing, should be captured in this C213 study if the subjects roll over to the TMC278IFD3004 study.
Unscheduled visits may be performed for safety/tolerability reasons, for reflex ACTH stimulation test in case basal cortisol is <248 nmol/L (<9 µg/dL) on initial and repeat testing, and for confirmation of plasma viral load results (see Section 6.4.1).

** For subjects who discontinue the trial before Week 48, this is the Withdrawal visit.

**** In the initial treatment period, the 4-week Follow-up visit is performed for subjects who withdraw early from the trial (i.e., before Week 48) (unless consent is withdrawn) or who do not participate in the extension after Week 48. In the extension period the 4-week Follow-up visit is only performed if there is an ongoing (S)AE, laboratory abnormality, or an increase in viral load at the last on-treatment visit. Additional unscheduled visits may be performed for safety/tolerability reasons, for reflex ACTH stimulation test in case basal cortisol is <248 nmol/L (9 µg/dL) on initial and repeat testing, and for confirmation of plasma viral load results.

a In case of suspected virologic failure (unconfirmed loss/lack of response, see Section 1) a sample for confirmation of plasma viral load and pharmacokinetics should be taken at an unscheduled visit (see Section 6.4.1).

b Samples collected at baseline, at virologic failure (see Section 6.2.5), at Week 48 and at the Final/Withdrawal visit will be tested for the determination of the HIV-1 genotype and phenotype, as long as the viral load is sufficiently high. Samples collected at other intervals may be selected for the determination of HIV-1 genotype and phenotype by the Protocol Virologist based on plasma viral load.

c Sample should be taken fasted (overnight).

d Any previously abnormal chemistry or hematology test should be repeated at this visit.

e Whenever possible, the ECG should be taken at expected C_{max} (i.e., 4 hours after intake of RPV).

f Assessment does not need to be performed at the withdrawal visit.

g A brief physical examination only.

h Growth will be followed using the standardized charts (see Section 6.4.9.4).

i Height does not need to be measured.

j As part of the evaluation of pubertal development, for girls who have not yet had their first menses at screening, it will be checked at every visit whether they have had their first menses and the date of first menses will be noted.

k Urine test for girls of childbearing potential.

l A pharmacokinetic sample will be taken at any time during the visit. The date and time of sampling and the date and time of the RPV intake prior to that sample should be recorded on the eCRF. Where possible (i.e., if RPV intake occurs during the visit), at least on one occasion, the sample will be taken just prior to RPV intake.

n Assessment of FSH, LH, androstenedione, testosterone, DHEAS, in conjunction with basal cortisol.

o **As of Amendment 10** this ACTH stimulation test is not scheduled at Week 24, but needs to be performed in case of confirmed abnormally low cortisol (<248 nmol/L [9 µg/dL]) or signs or symptoms of adrenal insufficiency (see Section 6.4.9.2.3.2).
ACTH stimulation test including measurements of cortisol and 17-hydroxyprogesterone, measured before (T0) and 60 minutes (T60) after ACTH stimulation, needs to be performed (see Section 6.4.9.2.3.2). The ACTH stimulation test needs to be conducted in the morning at the indicated visits, between 7h30 and 9h30. If ACTH stimulation test is abnormal (i.e., 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 (see Section 6.4.9.2.3.2). In case of withdrawal due to pregnancy, no ACTH stimulation test needs to be performed, but basal assessments need to be performed.

p Questionnaires will only be administered if a certified translation is available in the local language.

q Evaluation should be done according to local standard of care at the site (see Section 6.4.11 for details).

s AEs (including HIV-related events and the occurrence of AIDS-defining illnesses) and the intake of concomitant medication will be monitored throughout the trial from signing of the ICF onwards until the last trial-related activity.

t A PBMC sample will be taken to retrospectively characterize archived viral resistance.

u All study visits should be scheduled relative to the baseline visit date (eg, Day 1 + 56 days for Week 8) ± the allowed time window.

v Assessments not required for ongoing Cohort 2 subjects who are already in the post Week 48 treatment extension period **at the time of Amendment 10.**

2.2.2. Flowchart for Intensive Pharmacokinetic Sampling in Cohort 2

Note: As of Amendment 10 intensive pharmacokinetic sampling will take place for subjects with body weight <25 kg, after at least 2 weeks (between Day 14 and 18) of treatment with RPV and if a dose adjustment is required, after 14 to 18 days on the adjusted dose.

Subjects or their parent(s)/caregiver(s) should be contacted by telephone or email to assess adherence (to study drug and other ARVs) and to reinforce trial instructions every day for 3 days prior to the intensive pharmacokinetic visit. If the subject has missed a dose of RPV within 10 days prior to the intensive pharmacokinetic visit, the visit should be rescheduled so as to allow steady-state of RPV to be reached.

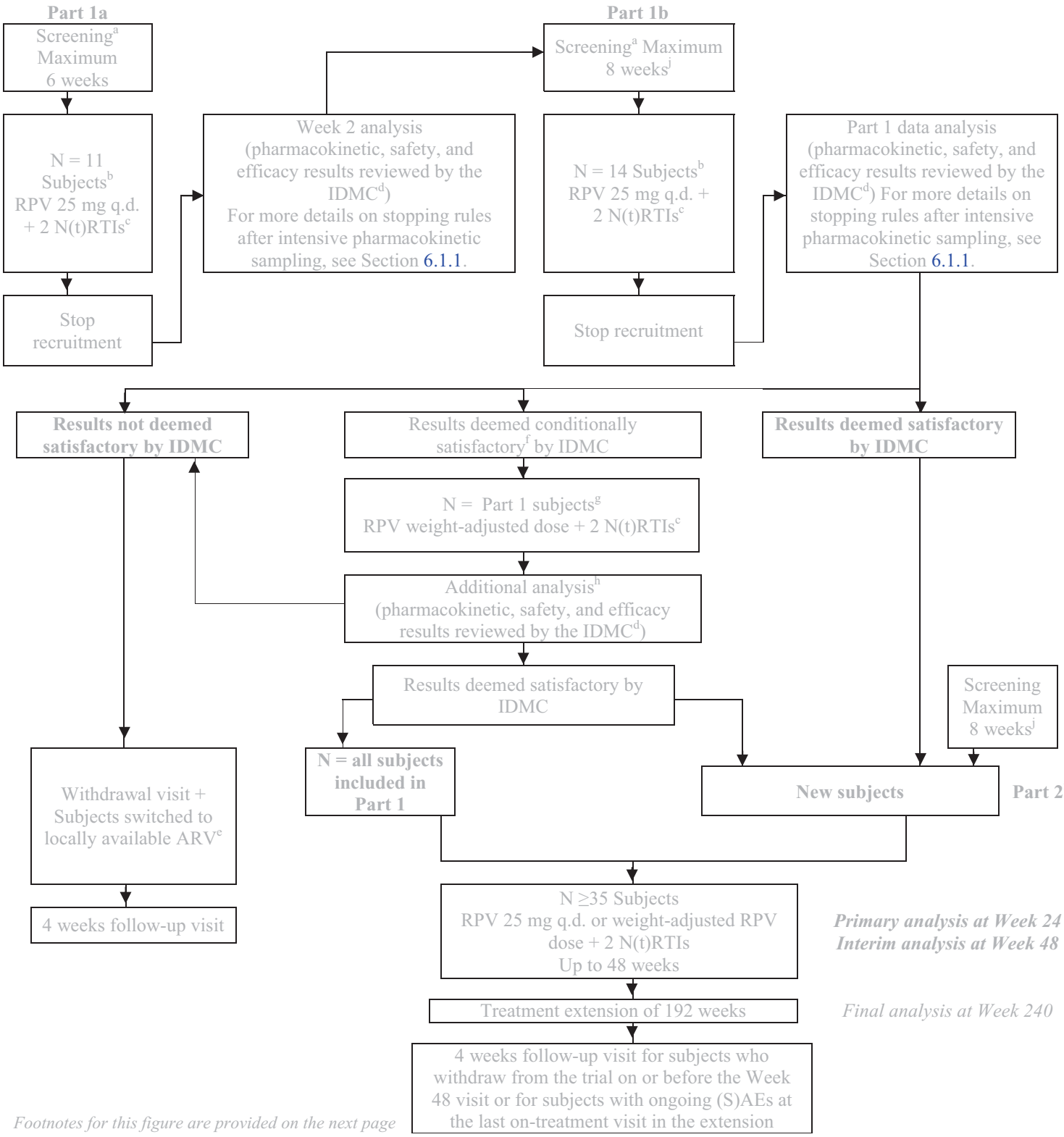
Subjects, their parent(s), or caregiver(s) will have to complete a diary documenting the intake of RPV from the start of treatment until the day of intensive pharmacokinetic sampling.

Time	Blood Sample[a]	ECG, Pulse Rate (PR), BP	Other
			Admission to unit
Predose	X[b]	X[c]	Age-appropriate standardized breakfast in unit
0 h			Intake RPV dose[e]
2 h	X		Resume usual diet
4 h	X	X[d]	
5 h	X		
6 h	X		
9 h[f]	X		
12 h[f]	X		
24 h[f]	X		Discharge from unit[g]

[a] At each time point, at least 1 mL of blood should be collected (total volume of blood drawn during the 24-hour period is approximately 10 mL).
[b] Within 1 hour before dosing.
[c] Within 2 hours before dosing.
[d] Only ECG should be performed at this time point (not PR and BP).
[e] RPV dose should be taken within 40 minutes following the start of the meal. For subjects who vomit within 30 minutes after dosing, the dose should be re-administered. Re-dosing is not allowed if the subject vomits more than 30 minutes after study drug intake. In the event that the subject vomits more than 30 minutes after the study drug intake on the day of pharmacokinetic evaluation, that assessment must be rescheduled.
[f] To allow for some flexibility, the 9-hour sample can be collected with a window of 8-10 hours postdose, the 12-hour sample within a window of 11-13 hours and the 24-hour sample with a window of 22-26 hours. The 24-hour sample must be collected prior to the next dose of RPV.
[g] In case it is not feasible for subjects to stay overnight, the subject can be discharged after the 12-hour sample. In this case, the subject should return to the unit for the 24-hour sample.

3. OVERVIEW OF TRIAL DESIGN

3.1. Cohort 1: Adolescent Subjects Aged ≥12 to <18 Years



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[a] To ensure that the duration between baseline and the review by the IDMC for subjects in Part 1a of Cohort 1 was kept as short as possible, investigators were to identify eligible subjects in advance. Recruitment was to be started when the majority of the sites had the necessary documentation and approvals in place and were therefore considered activated for enrollment. Recruitment of subjects for Part 1a has already been closed and the enrolled subjects can continue in the trial as judged by the IDMC.
For Part 1b, recruitment could start at the individual sites as soon as the necessary documentation and approvals were in place, and was closed once the required number of subjects was recruited. Trial sites were to be informed in advance regarding stop of recruitment.

[b] For Part 1a, at least 5 subjects in the age group ! 12 to <15 years and at least 5 subjects in the age group ! 15 to <18 years were to be recruited (simultaneously). Part 1a included 11 subjects, 4 subjects in the age group ! 12 to <15 years and 7 subjects in the age group ! 15 to <18 years. In Part 1b, approximately 12 subjects (in order to have at least 10 evaluable subjects at Week 4) were to be enrolled, aiming at an equal distribution of subjects between the two age groups (i.e., subjects ! 12 to <15 years of age and subjects ! 15 to <18 years of age). Part 1b included 14 subjects, 8 subjects in the age group ! 12 to <15 years and 6 subjects in the age group ! 15 to <18 years.

[c] Investigator-selected with a choice limited to AZT, ABC, or TDF in combination with 3TC or FTC, given as the co-formulation or as the separate components.

[d] Subjects included in the first part (Part 1) will continue their ARV regimen during this review period.

[e] In case Cohort 1 is stopped after Part 1, a sample will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ARV regimen. When determination of HIV-1 genotype on this sample is not possible due to a too low viral load, the new ARV regimen will be based on the screening HIV-1 genotyping result.

[f] Short-term Part 1 results show a safety concern that could potentially be avoided by lower exposure to RPV, as deemed by the IDMC.

[g] If applicable, RPV dose switch to weight-adjusted dose will be done for all Part 1 subjects up to a certain body weight.

[h] Analysis will be done when these subjects have been treated for 4 weeks (+/-1 week) with the weight-adjusted dose.

[i] In case a dose switch is not required, Part 2 will start immediately after the positive IDMC evaluation of the short-term Part 1 results. In case a dose switch is required, Part 2 will start after re-evaluation by the IDMC of the analysis when subjects have been treated for 4 weeks (+/-1 week) with the weight-adjusted dose.

[j] The screening period can be prolonged to maximum 8 weeks in order to allow plasma viral load and $CD4^+$ cell count to be assessed before continuing with the other screening assessments. After obtaining informed consent, samples will be taken for determination of plasma viral load and $CD4^+$ cell count. If plasma viral load results meet the inclusion criteria and the investigator considers initiation of ART appropriate (taking into account current treatment guidelines, including $CD4^+$ cell count and the subject's clinical situation), the subject 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 subject will be considered a screen failure.

3.2. Cohort 2: Pediatric Subjects Aged ≥6 to <12 Years

Prior to Amendment 10 Flow 1, as depicted below, was followed. All subjects enrolled in Cohort 2 at the time were treated with 25 mg RPV q.d., and since results of the Week 4 analysis were deemed satisfactory, no dose adjustments were required. These subjects are currently on 25 mg RPV q.d. as originally planned (no dose adjustments). Only limited data (i.e. 5 subjects) were available for subjects with body weight <25 kg.

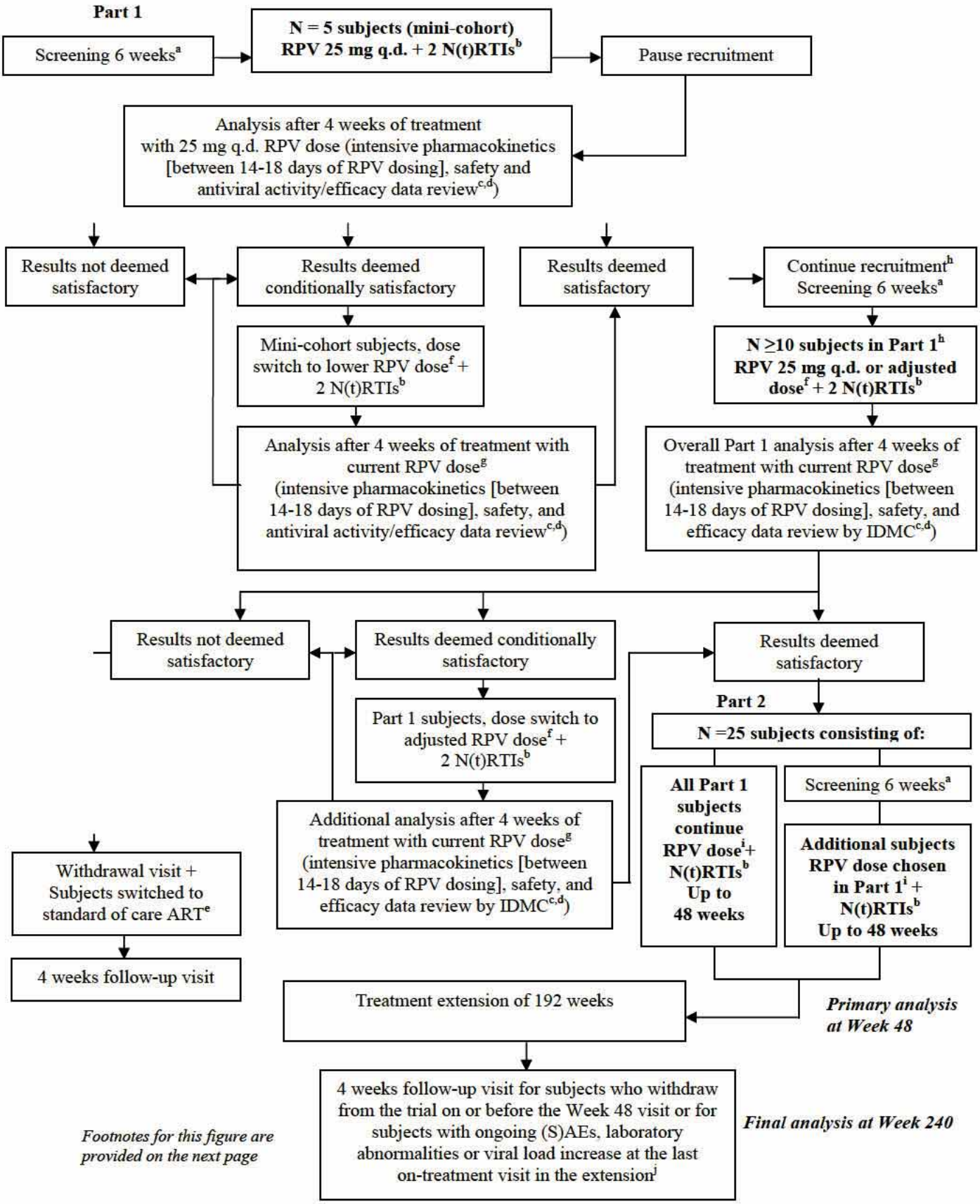
Based on accumulating data and PK modeling and simulation, **at the time of Amendment 10**, the following RPV dose recommendations were determined and endorsed by the IDMC for further enrolled subjects (aimed at achieving similar exposures as in adults):

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

Appropriateness of these doses will be further evaluated in this study in combination with data generated from pediatric study TMC278HTX2002. To this end, as depicted in Flow 2 below, newly enrolled subjects with a body weight of <25 kg will require intensive pharmacokinetic evaluation.

Note that **as of Amendment 10** the requirement for the 4-year follow-up period in this study for subjects enrolled in Cohort 2, has been removed.

Flow 1; Flow as was applicable prior to Amendment 10.



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[a] During the screening period it is allowed to assess the viral load and CD4+ cell count before continuing with the other screening assessments. In such case, after obtaining informed consent, samples will be taken for determination of plasma viral load and CD4+ cell count. If plasma viral load results meet the inclusion criteria and the investigator considers initiation of ART appropriate (taking into account current treatment guidelines, including CD4+ cell count and the subject's clinical situation), the subject will return within 2 weeks after availability of these results, for the remainder of the screening procedures. In case of unforeseeable circumstances, the screening period can be prolonged by 2 weeks resulting in a maximum screening period duration of 8 weeks, see Section 6.4.1.

[b] Investigator-selected with a choice limited to AZT, ABC, or TDF in combination with 3TC or FTC, given as a co-formulation or as separate components.

[c] Subjects will continue their ART during this review period.

[d] For details on dose evaluation criteria, see Section 6.1.1.2.1.

[e] In case Cohort 2 is stopped after Part 1, a sample will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ART. When determination of HIV-1 genotype on this sample is not possible due to a too low viral load, the new ART will be based on the screening HIV-1 genotyping result.

[f] All subjects who received the RPV dose which was not deemed satisfactory will receive an adjusted dose and undergo an intensive pharmacokinetic evaluation between 14 to 18 days after starting the adjusted dose. The results may indicate that only subjects up to e.g., a certain age or body weight would need a lower RPV dose in which case the subjects that do not need an RPV dose change will continue treatment with their current dose.

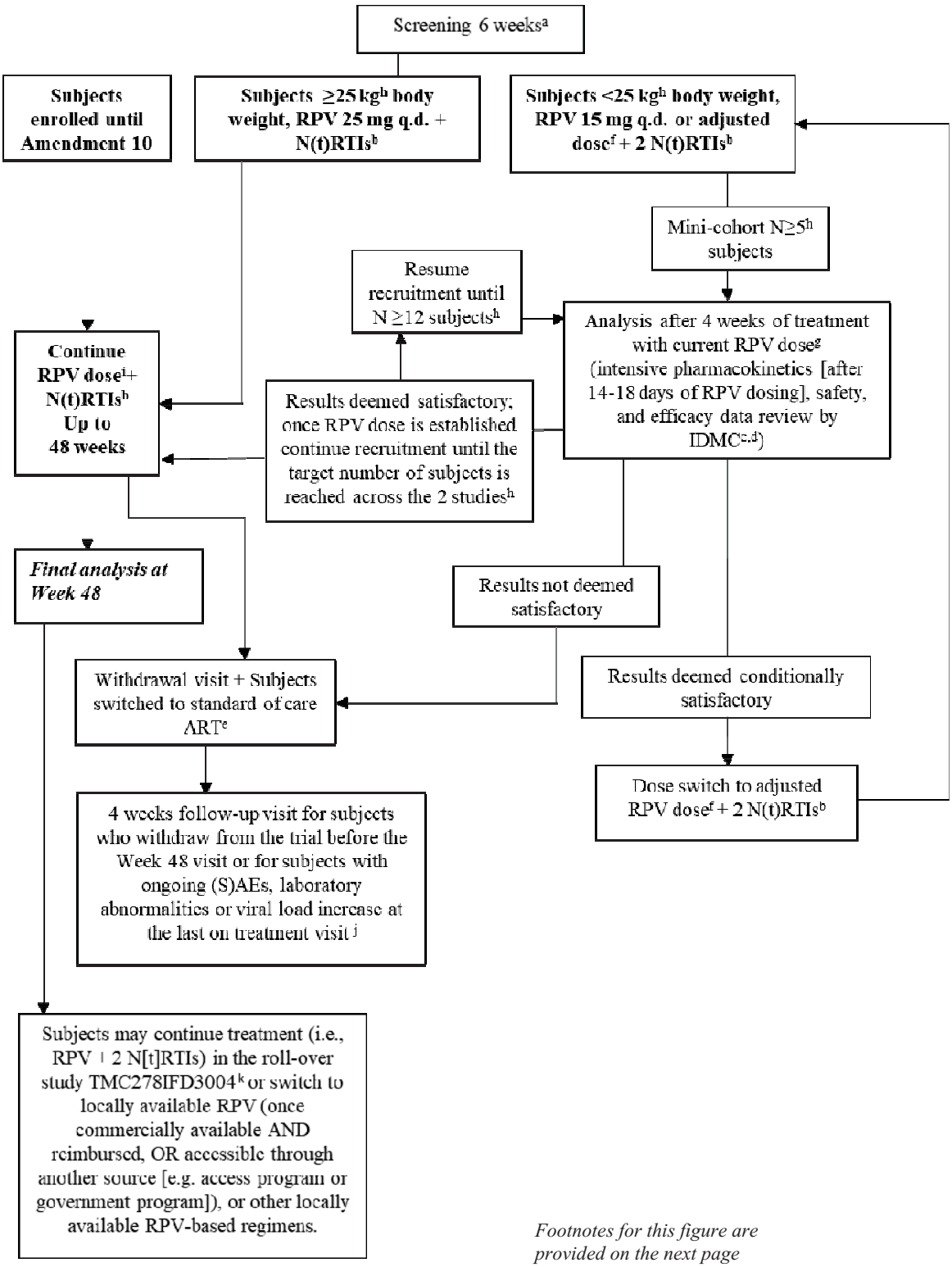
[g] Analysis will be done when all subjects in Part 1 have been treated for at least 4 weeks, or discontinued earlier with their current RPV dose (original and/or adjusted dose[s]).

[h] Additional subjects will be recruited to aim for at least 10 subjects with intensive PK data (including the subjects of the mini-cohort).

[i] Subjects in Part 2 will remain on the RPV dose established in Part 1 with no changes allowed in dosing except for adjustments due to age or body weight changes, if applicable.

[j] Additional unscheduled visits may be performed for safety/tolerability reasons and for confirmation of plasma viral load results.

Flow 2: Flow applicable **as of Amendment 10**.



Footnotes for this figure are provided on the next page

[a] During the screening period it is allowed to assess the viral load and CD4+ cell count before continuing with the other screening assessments. In such case, after obtaining informed consent, samples will be taken for determination of plasma viral load and CD4+ cell count. If plasma viral load results meet the inclusion criteria and the investigator considers initiation of ART appropriate (taking into account current treatment guidelines, including CD4+ cell count and the subject's clinical situation), the subject will return within 2 weeks after availability of these results, for the remainder of the screening procedures. In case of unforeseeable circumstances, the screening period can be prolonged by 2 weeks after screening tests have been performed, resulting in a maximum screening period duration of 8 weeks, see Section 6.4.1.

[b] Investigator-selected with a choice limited to AZT, ABC, or TDF in combination with 3TC or FTC, given as a co-formulation or as separate components.

[c] Subjects will continue their ART during this review period.

[d] For details on dose evaluation criteria, see Section 6.1.1.2.1.

[e] In case Cohort 2 is stopped, a sample will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ART. When determination of HIV-1 genotype on this sample is not possible due to a too low viral load, the new ART will be based on the screening HIV-1 genotyping result.

[f] All subjects who received an RPV dose which was deemed conditionally satisfactory (e.g. up to a certain body weight) will receive an adjusted dose and undergo an intensive pharmacokinetic evaluation between 14 to 18 days after starting the adjusted dose. Those that don't need dose adjustment, will continue their treatment.

[g] Analysis will be done combined with applicable data from the TMC278HTX2002 study, when all subjects have been treated for at least 4 weeks or discontinued earlier with their current RPV dose (original and/or adjusted dose[s]).

[h] Approximately 40 subjects will be enrolled in Cohort 2 and in pediatric study TMC278HTX2002 combined: at least 12 subjects with a body weight of <25 kg, including at least 7 subjects with a body weight of <20 kg.

[i] Subjects will remain on the RPV dose established with no changes allowed in dosing except for adjustments due to body weight changes, if applicable.

[j] Additional unscheduled visits may be performed for safety/tolerability reasons and for confirmation of plasma viral load results.

[k] Any retest of abnormal laboratory results or plasma viral load/resistance testing, should be captured in this C213 study if the subjects roll over to the TMC278IFD3004 study.

4. INTRODUCTION

Antiretroviral therapy in ARV-naïve children provides evidence that the combination of 2 NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) may reduce HIV RNA to undetectable levels in a substantial proportion of children[1,2].

Human immunodeficiency virus type 1 (HIV-1)-infected subjects are routinely being treated with combinations of 3 or 4 drugs (highly active ARV therapy [HAART]), including N(t)RTIs, NNRTIs, and protease inhibitors (PIs), to reduce the risk of viral resistance development. Development of new potent ARV compounds is urgently needed to prolong suppression of viral replication in subjects infected with HIV-1[1,2,3,51,52].

Approved NNRTIs in the United States of America (USA) and/or Europe are nevirapine (NVP; Viramune®), delavirdine (Rescriptor®), and efavirenz (EFV, Sustiva®, Stocrin®). These drugs show cross-resistance and are associated with safety problems (mainly hepatotoxicity, central nervous system symptoms, and/or rash)[3]. Etravirine (ETR, Intelence®), a NNRTI with a higher genetic barrier to the development of resistance, is approved for the use in treatment-experienced adults.

At the time of Amendment 6 writing, RPV (formerly known as TMC278 or R278474) has been approved for the treatment of HIV-1 infection in ARV treatment-naïve adult patients in multiple countries including the USA and European Union as EDURANT®. In most countries, including the USA and EU, this indication is further restricted to patients with a HIV-1 viral load ≤100,000 copies/mL.

Nevirapine is labelled for use in young children (aged 15 days and older) but has been shown to be inferior to lopinavir/ritonavir (LPV/r, Kaletra®)[49]. Efavirenz is approved for use in children from 3 months of age, but there are concerns about the approved dose such as risks to the fetus in females of childbearing age[50]. Etravirine is approved for ARV treatment-experienced children down to 6 years of age. A medical need still exists for development of new potent ARV compounds and age-appropriate formulations, particularly in adolescents and children. At the time of Amendment 9 writing, in several countries, including the USA and Europe, the indication of RPV has been extended to include adolescent patients aged ≥12 to <18 years of age, based on Week 48 data from Cohort 1 of the current study (see Section 6.1.2.2). Per the indication, RPV is approved for the treatment of HIV-1 infection in ARV treatment-naïve patients 12 years of age and older with a viral load ≤100,000 copies/mL. At the time of Amendment 9 writing, RPV was not approved in children <12 years of age.

RPV, a diarylpyrimidine derivative, is a potent NNRTI with in vitro activity against wild-type HIV-1 (50% effective concentration [EC_{50}] ranging from 0.30 to 0.73 nM for HIV-1/IIIb[4]) and NNRTI-resistant mutants. RPV is able to combine the convenience of once daily (q.d.) dosing with good antiviral effects and a good safety and tolerability profile as compared to most currently licensed NNRTIs (with the exception of ETR).

Non-clinical safety and toxicology studies demonstrated that RPV is safe for use in clinical testing[4]. In non-clinical studies in rats and dogs, changes in adrenal hormones and histopathology have been observed. In those studies, RPV appears to interfere with steroid biosynthesis, leading to decreases in cortisol and increases in progesterone and 17α-hydroxyprogesterone and as a result to increases in serum adrenocorticotropic hormone (ACTH). Preclinical work with RPV also identified changes in the thyroid glands in rats. Endocrine monitoring was included in the safety monitoring of all RPV clinical trials conducted thus far. However, to date, no clinically relevant effects on adrenal or thyroid function were observed in clinical studies with RPV in adults or adolescents.

The effects of RPV on adrenal glands of rats, dogs and cynomolgus monkeys on the estrous cycle of dogs are not expected to be clinically relevant for adolescents and children. However, in theory, some concerns in adolescents and children could be raised by these non-clinical findings: the possibility of partial adrenal insufficiency, virilization in girls and/or growth retardation due to 21-hydroxylase inhibition and precocious puberty due to ovarian stimulation in girls. In case significant inhibition of cortisol synthesis (partial adrenal insufficiency) would occur, androgen production might increase. In girls, this could result in masculinization and blunted growth. In boys, due to increased levels of testosterone, growth might also be impaired. Since the time of initial protocol writing, additional non-clinical information has become available in cynomolgus monkeys, which did not show evidence of induction of premature ovulation in juvenile animals. Refer to Section 6.1.2.2 for a brief summary of the non-clinical data on effects of RPV on adrenal and gonadal hormone biosynthesis. Therefore, in this trial, growth will be followed regularly and evaluated consistently using standardized growth charts. Sexual maturation will be evaluated according to Tanner stages. Finally, hormone testing will be performed, including measurements of testosterone, FSH, LH, cortisol, progesterone (only in the adolescent cohort), androstenedione, aldosterone (only in the adolescent cohort), DHEAS, and 17-hydroxyprogesterone.

Rilpivirine did not show a potential for genotoxicity, teratogenicity, phototoxicity, skin or mucous membrane irritation, or delayed-type sensitization. Fertility, early embryonic development, pre- and postnatal development, and the immune system were not affected by RPV at oral doses ranging from 160 to 1600 mg base eq./kg.

Results from previous pooled Phase I trials, in which 404 healthy adult subjects and 15 HIV-1 infected adults have been dosed with RPV, provided an understanding of the compound's short-term safety and efficacy profile, and its pharmacokinetic characteristics[4]. Two exploratory proof-of-principle (PoP) Phase IIa trials in 83 adults (47 ARV-naïve and 36 ARV-experienced) were performed to evaluate the short-term antiviral and immunologic activity during a 7-day once daily treatment up to 150 mg RPV[5,6]. One Phase IIb trial (i.e., TMC278-C204) in which 368 ARV-naïve HIV-1 infected adults were included, has been completed and was set up to evaluate the dose-response relationship of efficacy over 96 weeks of treatment with 3 different dose regimens (25 mg q.d., 75 mg q.d., and 150 mg q.d.) of RPV. The trial has been extended to a total treatment duration of 240 weeks in order to collect long-term efficacy and safety data from

subjects who continue to benefit from their treatment. After 240 weeks of treatment, continued access to RPV is foreseen in another trial or program, until RPV becomes commercially available, is reimbursed, or can be accessed through another source. All RPV-treated subjects were switched to RPV 25 mg q.d. (the dose selected for further development) at approximately Week 144, but no later than Week 157, and continued on this dose for the remainder of the trial. Data from the primary analysis at 48 weeks and the analyses at 96, 144, 192, and 240 weeks of treatment in this trial are available[7,8]. These data showed that RPV was generally safe and well tolerated after long-term treatment. This was confirmed by final data of two completed Phase III trials in ARV treatment-naïve HIV-1 infected adults. These trials were set up to evaluate long-term efficacy, safety, and tolerability of RPV 25 mg q.d. versus efavirenz 600 mg q.d. (each in combination with 2 N[t]RTIs).

Rilpivirine, formulated as a tablet, was well absorbed after oral administration in humans. The time to reach the maximum plasma concentration (t_{max}) was consistently around 4 hours in all trials. The terminal elimination half-life ($t_{1/2,term}$) was approximately 45 hours across trials, supporting q.d. administration. Renal clearance is only a minor route for the elimination of RPV[4].

The relative oral bioavailability of RPV formulated as a tablet increased approximately 1.5-fold when administered with food as compared to administration under fasted conditions. RPV, administered as the Phase II tablet formulation, exhibited linear pharmacokinetics for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) in healthy subjects after single- and multiple-dose administration up to a dose of 150 mg q.d.[4]

The relative oral bioavailability of RPV as the Phase III tablet formulation was shown to be comparable to that of the Phase II tablet. These results support the use of the Phase III tablet formulation for the further clinical development of RPV[9].

The safety data from the pooled Phase I studies showed that RPV was generally safe and well tolerated after multiple dosing in adults up to 150 mg q.d. for 14 days[4]. The 2 PoP Phase IIa trials[5,6] demonstrated the safety and efficacy of RPV in HIV-1 infected subjects who were ARV-naïve as well as in HIV-1 infected subjects who were failing either an NNRTI- or PI-containing (with evidence of resistance to the current NNRTIs) therapy.

The primary analysis of the Phase III, randomized, double-blind, double dummy, active-controlled trials in adults with RPV (i.e., TMC278-TiDP6-C209 and TMC278-TiDP6-C215) was conducted when all subjects had reached Week 48 or discontinued earlier. In total, 1,368 subjects who were randomized and received at least one dose of study drug were included in this analysis: 686 subjects in the RPV group and 682 subjects in the control group on efavirenz[41,42]. The primary analysis (pooled) of these trials at 48 weeks showed non-inferiority of RPV versus control with response rates of 84.3% and 82.3% in the RPV and the control group, respectively, for the primary efficacy parameter (confirmed and sustained plasma viral load <50 HIV-1 RNA copies/mL according to the time to loss of virologic response [TLOVR]

algorithm)[43]. The rate of virologic failure was shown to be dependent on the baseline viral load, with a higher rate of virologic failure in the >100,000 copies/mL category (15.1% in the RPV group and 6.3% in the control group) than in the ≤100,000 copies/mL category (3.8% in the RPV group and 3.3% in the control group). The effect of baseline viral load was more pronounced in the RPV group than in the control group (i.e., 2- to 3-fold higher rate of virologic failure in the >100,000 copies/mL category in the RPV group compared to control)[45]. RPV was generally safe and well tolerated up to Week 48. The most common adverse events (AEs) in the RPV group according to the pooled Phase III Week 48 analysis were headache (13.8%), nausea (13.4%), diarrhea (11.4%), and nasopharyngitis (10.1%).[44]

At the time of protocol amendment 6 writing, both Phase III trials had been completed. The data of these trials show that RPV was efficacious, generally safe and well tolerated after 96-weeks of treatment. No new safety signals were observed between the first 48-weeks of treatment (primary analysis) and the end of the trial. A brief summary of the final Phase III results in adults is presented in Section 6.1.2.2.

In accordance to the International Conference on Harmonization (ICH) E14 guideline[10], a thorough QT trial in adults (TMC278-TiDP6-C131) was carried out[11]. At a dose of RPV 75 mg q.d., a clinically relevant increase of the QTc interval by up to 10.4 ms (90% confidence interval [CI]: 7.7 ms; 13.1 ms) as compared to reference (i.e., baseline) was observed and the effect was dose- and concentration-dependent, with a higher increase at higher exposures obtained with a dose of 300 mg q.d. (i.e., up to 23.8 ms [19.8 ms; 27.8 ms] compared to reference). Besides these recent findings in the thorough QT trial, all single dose as well as multiple-dose trials with RPV in healthy subjects showed no consistent or clinically relevant changes in any particular ECG parameter, including the QTc interval. Also in HIV-1 infected subjects in short-term PoP trials and the Phase IIb trial, the observed changes in ECG parameters are not clinically relevant. In the Phase IIb trial, up to Week 96, 3 female subjects were discontinued from the trial because of QTcF prolongation (grade 2-3, all considered related to RPV), but without clinical symptoms[7]. No clinically relevant findings in ECG parameters have been seen up to now, but, besides the thorough QT trial, these trials were not specifically designed to study the effect on cardiac electrophysiology in healthy or HIV-1 infected subjects. No sudden deaths or life-threatening dysrhythmias such as Torsade de Pointes have been observed in any of the trials. Based on pharmacokinetic/pharmacodynamic modeling it was predicted that RPV 25 mg q.d. would not have a clinically relevant effect on QTc. This assumption was confirmed in a pilot QT trial[12] and a thorough QT trial[20], specifically designed to explore the effect of steady-state concentrations of RPV 25 mg q.d. on the QT/QTc interval: the 25 mg q.d. dose used in these trials did not cause a clinically relevant QT prolongation, hence the 25 mg q.d. dose of RPV is suitable for further development.

RPV 25 mg q.d. was the dose used in the Phase III trials and therefore also the reference dose for the pediatric development. For the most current information and additional details on characteristics, non-clinical or clinical data, please consult the Investigator's Brochure[4]. A summary of new clinical data, relevant to this trial, can also be found in Section 6.1.2.2.

The current trial is the first to be conducted with RPV in the adolescent population (Cohort 1). The purpose of the present trial is first to compare the short-term steady-state RPV pharmacokinetics in a small group of ARV treatment-naïve subjects aged ! 12 to <18 years with that in the adult population (in trials TMC278-C204, TMC278-TiDP6-C209, and TMC278-TiDP6-C215), as well as to evaluate short-term safety and antiviral activity of RPV in the adolescent population (Part 1). If the short-term results of Part 1 are deemed satisfactory by the Independent Data Monitoring Committee (IDMC), long-term treatment will be evaluated in a larger group of subjects aged ! 12 to <18 years in the second part of this cohort (Part 2). At the time of protocol amendment 6 writing, 48-week results from this adolescent cohort are available. The 48-week results demonstrated that treatment with RPV 25 mg q.d., in combination with an investigator-selected background regimen, is efficacious, generally safe and well tolerated in adolescents of ≥12 to <18 years of age. For more details about the 48-week results see Section 6.1.2.2, the clinical study report of Cohort 1[53] or the abstract[54]. These 48-week treatment results are considered adequate to start treatment in children <12 years of age and therefore the protocol has been amended.

In addition to adolescents (Cohort 1), the trial was extended to include children ≥6 to <12 years of age (Cohort 2). In Part 1 of this cohort, the short-term steady-state RPV pharmacokinetics in a group of ARV treatment-naïve subjects aged ≥6 to <12 years were compared with that in the adult population, and an evaluation of safety, tolerability and antiviral activity/efficacy of RPV in these children was done.

At the time of Amendment 10, the following RPV dose recommendations were determined based on accumulating data and were endorsed by the IDMC, in order to achieve similar exposure to RPV compared to adults: RPV 25 mg q.d. for subjects with a body weight of ≥25 kg, and RPV 15 mg q.d. for subjects with a body weight of <25 kg. Appropriateness of these doses will be further evaluated in this study.

It is recognized that the pediatric age group deserves specific attention, both towards more intense compliance counseling and, especially for the adolescents, towards sexual behavior and risk of HIV transmission. Specific sections in the protocol will address these.

5. OBJECTIVES

The objectives are:

- To evaluate the steady-state pharmacokinetics (based on intensive PK analysis) of RPV 25 mg q.d. or adjusted dose of RPV (q.d.) in subjects aged ! 12 to <18 years and ! 6 to <12 years;
- to evaluate short-term safety, tolerability and antiviral activity/efficacy of RPV in these age groups.
- To evaluate safety, tolerability and efficacy of RPV over a 24-week (Cohort 1 only) and 48-week (Cohort 1 and 2) treatment period;

- to evaluate immunologic changes (as measured by $CD4^+$ cell parameters) over 24 weeks (Cohort 1 only) and 48 weeks (Cohort 1 and 2) of treatment with RPV;
- to assess the evolution of viral genotype and phenotype over 24 weeks (Cohort 1 only) and 48 weeks (Cohort 1 and 2) of treatment with RPV;
- to evaluate pharmacokinetics (by means of population pharmacokinetics) and pharmacokinetic-pharmacodynamic relationships for safety and efficacy of RPV;
- to evaluate treatment adherence as measured by the Study Adherence Questionnaire for Children and Teenagers (see Addendum 7: Study Adherence Questionnaire for Children and Teenagers).
- To evaluate the safety, tolerability and efficacy of RPV for up to 240 weeks of treatment (Cohort 1 only).

6. METHODS

Details on the treatment and assessments are given in the flowchart (see Section 2).

6.1. Trial Design

6.1.1. Overview of Trial

This is a Phase II, open label, single arm trial to evaluate the pharmacokinetics, safety, tolerability and efficacy of RPV 25 mg q.d. or adjusted dose of RPV (q.d.) in combination with an investigator-selected background regimen containing 2 N(t)RTIs (AZT, ABC, or TDF in combination with 3TC or FTC, age-appropriate formulations are to be used), in ARV treatment-naïve adolescents and children aged ! 6 to <18 years.

6.1.1.1. Cohort 1: Adolescents Aged ≥12 to <18 Years

ARV treatment-naïve HIV-1 infected subjects, aged ! 12 to <18 years, with a plasma viral load ! 5,000 HIV-1 RNA copies/mL could be included in Part 1a of Cohort 1. However, in Part 1b and Part 2, recruitment was limited to subjects with a plasma viral load ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL. Any previous use of ARVs, with the exception of a single dose of NVP at birth to prevent mother-to-child transmission (MTCT), is not allowed. Subjects who were infected by MTCT are allowed to enter, provided the mother was ARV treatment-naïve at the time of delivery with the exception of NVP monotherapy for no more than 3 days. Subjects should have no NNRTI resistance-associated mutations (RAMs) on their screening HIV-1 genotyping result (exclusion based on the list of NNRTI RAMs detailed in Section 6.2.3). ABC has been associated with severe hypersensitivity reactions, and the risk for developing such reactions has been linked to the presence of the HLA-B*5701 allele. Therefore, subjects without prior documented HLA-B*5701 negative results for whom the investigator considers to use ABC/3TC as background regimen should test negative for HLA-B*5701 at screening, to avoid hypersensitivity reactions (see Section 6.5.11.3 for details).

Subjects willing and able to give consent (in case the subject's age is below the cut-off age for consent [according to local regulations], their parent/caregiver should be able and willing to give consent, and the subject will be informed about the trial and asked to give positive assent) and found eligible for the trial at screening, will be required to discontinue specified disallowed medication to allow a washout period of at least 4 weeks prior to baseline. Assessments at screening will be performed as indicated in the flowchart (see Section 2).

The trial will consist of a screening period of maximum 8 weeks (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 assessment, if these were assessed separately before continuing with the other screening assessments, but in case of unforeseeable circumstances, this period can be prolonged by 2 weeks maximum), an initial treatment period of 48 weeks, and a post Week 48 treatment extension period of 4 years. Subjects who withdraw from the trial on or before the Week 48 visit

or subjects with ongoing (S)AEs at the last on-treatment visit in the extension, will be seen for a follow-up visit 4 weeks later.

Recruitment and analyses of the initial 48-week treatment period will be structured into 2 parts (for a flowchart of the trial visits, see Section 2).

The **first part of Cohort 1** (Part 1, consisting of Part 1a and Part 1b) is designed to evaluate the steady-state pharmacokinetic profile and the short-term safety and antiviral activity of RPV 25 mg q.d. when administered in combination with 2 N(t)RTIs, in adolescents. In Part 1a, a group of at least 10 subjects, i.e., at least 5 subjects in the age group ! 12 to <15 years and at least 5 subjects in the age group ! 15 to <18 years, were to be enrolled and to receive treatment. Eventually, 11 subjects were enrolled, 4 subjects in the age group ≥12 to <15 years and 7 subjects in the age group ≥15 to <18 years, and enrollment was paused at that time. At Week 2, an analysis for pharmacokinetics together with short-term safety and antiviral activity was reviewed by an IDMC (for more information on this IDMC, see Section 6.3.9). Based on these Week 2 data the IDMC agreed for these subjects to continue treatment with RPV 25 mg q.d. and their background regimen. Following the review of the 2-week interim results in adolescents and the available Phase III results in adults, the Sponsor decided to collect more short-term data in adolescents before proceeding with the second part of Cohort 1 (Part 2). Therefore, Part 1 was expanded by enrolling approximately 12 additional subjects (in order to have at least 10 evaluable subjects at Week 4) in Part 1b, aiming at an equal distribution of subjects between the two age groups (i.e., subjects ≥12 to <15 years of age and subjects ≥15 to <18 years of age). Eventually, 14 subjects were enrolled in Part 1b, 8 subjects in the age group ! 12 to <15 years and 6 subjects in the age group ! 15 to <18 years, to a total of 25 subjects enrolled in Part 1. In Part 1b, only subjects with a screening viral load ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL were to be enrolled. The 4-week interim analysis of Part 1b was evaluated by the IDMC before the start of Part 2. The results indicated that no RPV dose adjustment was needed.

When reviewing the Part 1 results, the IDMC took into account the guidelines and stopping rules mentioned below.

- If the mean steady-state exposure of RPV in Part 1 subjects is comparable to that of the adult population (i.e., is within 80-125% of the mean exposure of the 25 mg q.d. dose group in available trials in HIV-infected adults) and the short-term safety and antiviral activity results have been reviewed and deemed satisfactory by the IDMC, the second part of Cohort 1 will start.
- However, if the mean exposure in adolescents is <80% of the mean exposure in adults or the Week 2/Week 4 results are not deemed satisfactory, all subjects will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to a locally available ARV regimen, and the trial will be stopped. In this case, a sample will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral

load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ARV regimen. When determination of HIV-1 genotype on this sample is not possible due to a too low viral load, the new ARV regimen will be based on the screening HIV-1 genotyping result.

- If the mean exposure in adolescents is >125% of the mean exposure in adults, but antiviral activity results are satisfactory and there are no safety concerns, as judged by the IDMC, the second part of Cohort 1 will start.
- If the mean exposure in adolescents is >125% of the mean exposure in adults, the antiviral activity is satisfactory, but there are safety concerns that could potentially be avoided by a lower exposure to RPV, as judged by the IDMC, subjects up to a certain body weight (determined based on the intensive pharmacokinetic results) will be switched to a lower, weight-adjusted dose; subjects who do not require a dose switch will continue treatment with RPV 25 mg q.d. A new analysis will be performed when all subjects on the weight-adjusted dose have been treated for 4 weeks (+/-1 week). When these results are deemed satisfactory by the IDMC, these subjects will continue treatment with RPV at the weight-adjusted dose and the second part of Cohort 1 will start.

All subjects in Part 1 were to continue their ART (RPV plus an investigator-selected background regimen of 2 N[t]RTIs) during the review period by the IDMC. For more information, see Section 6.1.2.

To ensure that the duration between baseline and the review by the IDMC for subjects in Part 1a was kept as short as possible, investigators were to identify eligible subjects in advance. Recruitment was to be started when the majority of the sites had the necessary documentation and approvals in place and were therefore considered activated for enrollment. Recruitment of subjects for Part 1a has already been closed and the enrolled subjects can continue in the trial as judged by the IDMC. For Part 1b, recruitment could start at the individual sites as soon as the necessary documentation and approvals were in place, and was completed once the required number of subjects was recruited. Trial sites were informed in advance regarding stop of recruitment.

In case of inadequate exposure, dose adjustments of RPV cannot be allowed in order to avoid exposing children to a daily dose exceeding the total adult daily dose (i.e., 25 mg q.d.).

The **second part of Cohort 1** will evaluate long-term safety, efficacy, and pharmacokinetics of RPV in combination with a background regimen of 2 N(t)RTIs, in a total of at least 35 adolescents (approximately 12 female subjects will be targetted). All subjects initially enrolled in Part 1 were to continue the initial treatment period until they reach a treatment duration of 48 weeks. Additional subjects were recruited with a screening viral load ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL, so that at least 35 subjects were enrolled and also received initial treatment for 48 weeks. The additional subjects were only be recruited after the IDMC had decided that this second part of Cohort 1 could start.

Subjects who experience and are expected to continue experiencing clinical benefit from RPV and the background regimen comprising 2 N(t)RTIs at the end of the initial 48-week treatment period, will have the option to continue treatment (i.e., RPV 25 mg q.d. + 2 N[t]RTIs) through this trial for an additional 4 years in a post Week 48 treatment extension period. During this treatment extension, trial visits will occur approximately every 3 months.

Formal analyses (with formal database lock) will be performed when all subjects have reached Week 24 (or discontinued earlier) (primary analysis time point), when all subjects have reached Week 48 (or discontinued earlier), and when all subjects have completed the trial (after 240 weeks of treatment) (or discontinued earlier). Furthermore, data monitoring for risk-benefit assessment was to be performed when all Part 1 (i.e., Part 1a and Part 1b) subjects had reached Week 12 (or discontinued earlier) and will be performed when all Part 1 and Part 2 subjects have reached Week 12 of treatment (or discontinued earlier). These analyses will be run based on the accumulated data at that point. The results of all analyses up to Week 48 will be shared and discussed with the IDMC.

The design of the trial is illustrated in Section 3.

For eligible subjects, the trial will be initiated on Day 1. In both Part 1 and Part 2, as well as in the post Week 48 treatment extension, the ARV regimen will consist of RPV 25 mg q.d. or weight-adjusted dose, and an investigator-selected background regimen containing 2 N(t)RTIs. The investigator-selected N(t)RTIs will be AZT, ABC, or TDF in combination with 3TC or FTC, whichever is approved and marketed or considered local standard of care for children aged ! 12 to <18 years in a particular country. The background regimen will be given as the co-formulation or as the separate components, according to local availability and use in the country (e.g., Combivir® or AZT/3TC, Epzicom®/Kivexa® or ABC/3TC, Truvada® or TDF/FTC). For those subjects who do not tolerate the selected N(t)RTIs, switching to alternative N(t)RTIs (brand name versions, US FDA tentatively approved generics, WHO prequalified drugs and if not available, exceptionally generic drugs approved by local Health Authorities or drugs procured by UN international organizations upon approval by the sponsor) is allowed for some predefined toxicities (see Section 6.3.5). At all times, the background regimen should consist of 2 N(t)RTIs and the subject's HIV-1 genotype at screening should show sensitivity to the alternative N(t)RTIs. Also in case of switch to ABC, the subject should test negative for HLA-B*5701, to limit the risk of hypersensitivity reactions (in case no prior documented HLA-B*5701 negative results are available) (see Section 6.5.11.3). The symptoms of intolerance to the N(t)RTI(s) should be reported as AE(s) and should be clearly documented as leading to the change in N(t)RTIs. If the tolerability issue is related to only 1 of the 2 N(t)RTIs, it is only needed to switch that one. The use of PIs, NNRTIs (other than RPV), enfuvirtide (ENF), integrase inhibitors, and investigational ARVs during the trial is not allowed.

In the second part of Cohort 1 temporary interruption of all ARVs during the treatment period will be allowed in the event of suspected toxicity, as long as the temporary interruption is associated with and can be linked to an AE or a serious AE (SAE) and this is not one of the cases

listed in Section 6.2.5 or Section 6.5. The maximum allowed duration of a single treatment interruption for toxicity reasons will be 4 weeks and the maximum allowed cumulative duration of the treatment interruptions for toxicity reasons will be 8 weeks (interruptions are counted cumulatively within a time frame of 48 weeks). Subjects should maintain the regular visit schedule during the treatment interruptions. Additional unscheduled visits may be performed for safety or tolerability reasons. Re-initiation of therapy including the background regimen will only be allowed once the event has resolved or decreased to a grade 2 or below. A subject must be withdrawn from the trial in case the total cumulative duration of treatment interruptions for suspected toxicities is more than 8 weeks (interruptions are counted cumulatively within a time frame of 48 weeks) or the duration of a single treatment interruption for a suspected toxicity is more than 4 weeks (see Section 6.2.5). Special considerations may be warranted for the discontinuation of certain ARV agents (see Section 6.3.5).

During the treatment period, the subject will have regular visits as stated in the flowchart (Section 2) during which the investigator will assess the subject's medical condition, virologic and immunologic response, any AEs, safety and tolerability issues (including blood and urine tests) and study drug compliance, and during which pharmacokinetic samples will be taken. The subject and/or their parent(s) or caregiver(s) will also complete a compliance questionnaire (Study Adherence Questionnaire for Children and Teenagers, Addendum 7; and Study Adherence Questionnaire for Caregivers, Addendum 8). Subjects included in Part 1, or their parent(s) or caregiver(s), additionally were to complete a diary documenting the intakes of RPV from the start of treatment with RPV 25 mg q.d. or weight-adjusted dose until the day of intensive pharmacokinetic sampling.

Details on the timing of the treatments and assessments are given in the flowchart (Section 2) and in Section 6.4.

Subjects who withdraw from the trial early (i.e., before the Week 48 visit) or subjects who do not participate in the extension after Week 48, will be seen for a follow-up visit. In the extension period, the 4-week follow-up visit is only performed if there is an ongoing (S)AE at the last on-treatment visit.

After 240 weeks of treatment, continued access to RPV is foreseen in an open label roll-over trial until RPV becomes commercially available, is reimbursed or can be accessed through another program. Provision of study drug will be stopped in case subjects cease to benefit from the treatment or when development of RPV is discontinued.

Note: At the time of protocol amendment 6 writing, 48-week results from the adolescent cohort were available and a summary of these results has been provided in Section 6.1.2.2. For more details refer to the clinical study report of Cohort 1[53] or the abstract[54].

6.1.1.2. Cohort 2: Children Aged ≥6 to <12 Years

In Cohort 2 of the trial, ARV treatment-naïve HIV-1 infected subjects aged ≥6 to <12 years with a plasma viral load ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL will be included. Any previous use of ARVs, with the exception of a single dose of NVP at birth or up to 6 weeks of AZT use to prevent MTCT, is not allowed. The same exclusion criterion related to NNRTI RAMs (see Section 6.2.3) and precautions related to ABC use applies as in adolescents in Cohort 1 (see Section 6.5.11.3). For a list of all inclusion and exclusion criteria see Section 6.2.2 and 6.2.3. For a list of specific guidelines regarding use of prior and concomitant therapy (see Section 6.3.13). For more information about the visit schedule of Cohort 2 see the flowcharts in Section 2.2.

To accommodate regulatory requirements concerning the evaluation of RPV in the pediatric population, overall across studies C213 (Cohort 2; children aged ≥6 to <12 years) and TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥11 kg), approximately 40 subjects will be enrolled of which at least 12 subjects with a body weight of <25 kg, including at least 7 subjects with a body weight of <20 kg. The PK data from Cohort 2 will be combined with the data from pediatric study TMC278HTX2002.

The analysis of the first 10 subjects in Cohort 2, including PK modeling and simulation to further assess the RPV pediatric dose based on accumulating data, was discussed with and endorsed by the IDMC. With this, **at the time of Amendment 10**, the following RPV dose recommendations will apply to newly enrolled subjects:

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

All ongoing subjects in Cohort 2 (who are already in the post Week 48 treatment extension period **at the time of Amendment 10)** will remain on the RPV 25 mg q.d. dose + 2 N(t)RTIs (investigator-selected), until their roll-over to study TMC278IFD3004 has been completed (see addendum 7.11). All newly recruited subjects will start treatment with the weight-appropriate RPV dose stated above + 2 N(t)RTIs (investigator-selected), until they reach a total treatment duration of 48 weeks or discontinue earlier. If newly recruited subjects with a body weight of <25 kg, increase in weight such that they require a 25 mg RPV dose, they can change to the 25 mg tablet formulation.

To further evaluate and confirm the RPV dose for subjects with lower body weight, newly enrolled subjects with a body weight of <25 kg require intensive PK evaluation. An overall analysis of the intensive pharmacokinetic data and all available safety, tolerability and antiviral activity/efficacy data will be reviewed by the Sponsor and the IDMC to assess appropriateness of the dose (see section 6.1.1.2.1 for dose evaluation criteria).

- If the results are not deemed satisfactory, and no alternative RPV dose seems feasible, all subjects will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to local standard of care, and Cohort 2 will be stopped.

- If the results are not deemed satisfactory but concerns can be addressed by adjusting the RPV dose (doses of >25 mg q.d. are not allowed) for certain subjects (e.g. up to a certain body weight), those subjects will be switched to an adjusted dose, while those that don't need dose adjustment, will continue their treatment. For all subjects who require an RPV dose adjustment, a 24-hour intensive pharmacokinetic evaluation after 14 to 18 days on the adjusted dose will be performed. After the subjects have been treated with the adjusted RPV dose for at least 4 weeks or discontinued earlier, an analysis of the intensive pharmacokinetic data (after 14 to 18 days of RPV dosing), and all available safety, tolerability and antiviral activity/efficacy data will be reviewed. If, after review of the data, the RPV dose is still not acceptable, the process will be repeated until an acceptable RPV dose is found or it is deemed necessary to stop Cohort 2.

Note: If in the mini-cohort, subjects discontinue the trial before receiving their first dose of study drug, additional subjects can be recruited to have 5 subjects with a body weight of <25 kg starting treatment in the mini-cohort. If subjects discontinue the trial after starting treatment for reasons other than drug tolerability/safety, additional subjects can be recruited to have at least 12 subjects with a body weight of <25 kg with intensive pharmacokinetic data. Additional subjects may also be recruited if the Sponsor and the IDMC deem it necessary to have additional subjects with intensive pharmacokinetic data because interpretation of the data is hampered by e.g., study drug adherence issues prior to the intensive pharmacokinetic sampling time point.

Subjects who experience and are expected to continue experiencing clinical benefit from RPV and their background regimen comprising 2 investigator-selected N(t)RTIs at the end of the initial 48-week treatment period, may continue treatment (i.e., RPV + 2 N[t]RTIs) in the roll-over study TMC278IFD3004 or switch to locally available RPV (once commercially available AND reimbursed, OR accessible through another source [e.g. access program or government program]), or other locally available RPV-based regimens. Any retest, of abnormal laboratory results or plasma viral load/resistance testing, should be captured in this C213 study if the subjects roll over to the TMC278IFD3004 study.

Formal analyses (with formal database lock) will be performed when all subjects have reached Week 48, or discontinued earlier (primary analysis). Furthermore, data monitoring for risk-benefit assessment (no formal database lock) will be performed when all subjects in this C213 study reach Week 12 and Week 24, or discontinued earlier. These analyses will be based on the accumulated data at that point. The results of all analyses up to Week 48 will be shared and discussed with the IDMC. Analyses (no formal database lock) will also be performed for subjects with body weight <25 kg (mini-cohort and full group of subjects with body weight <25 kg) for dose finding purposes when the subjects have been treated for at least 4 weeks, or discontinued earlier, with the original and/or adjusted dose. These analyses for dose finding purposes will be based on the intensive pharmacokinetic data after 14 to 18 days of treatment with the original and/or adjusted RPV dose and all available safety, tolerability and antiviral activity/efficacy data. Results of these intensive pharnacokinetic analyses, and if applicable,

analyses after RPV dose adjustments will be shared and discussed with the IDMC. For more details about the analyses, see Section 6.6.

The design of the trial is illustrated in Section 3.2.

Information on the study drug and investigator-selected background regimen can be found in Sections 6.3.1 and 6.3.2. Guidance on temporary interruptions and switching to alternative N(t)RTIs in case of toxicities can be found in Sections 6.3.5 and 6.5.11.3, and information on study drug discontinuation or removal of the subject from the trial can be found in Section 6.2.5. Details about the treatment duration and assessments to be performed during the trial are provided in the flowcharts in Section 2 and in Section 6.4.

The total blood volume to be collected in this pediatric study has been optimized as much as possible, considering the safety assessments required in this clinical study, and the pharmacokinetic analysis necessary for establishing the appropriate dose. The sponsor considers the total blood quantity drawn clinically acceptable, in view of the age span of the children included in the study i.e., between ≥6 to <12 years old[57].

After 48 weeks of treatment, continued access to RPV is foreseen in the roll-over study TMC278IFD3004 or by switching 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. Provision of study drug will be stopped in case subjects cease to benefit from the treatment or when development of RPV is discontinued.

6.1.1.2.1. Dose Evaluation Criteria for Cohort 2

AUC_{24h} of a selected RPV dose under fed and steady-state conditions will be the primary pharmacokinetic parameter for determination of the acceptability of the RPV dose. The target geometric mean RPV AUC_{24h} is between 80% and 150% of the observed geometric mean AUC_{24h} for RPV in HIV-1 infected adults from the Phase III pharmacokinetic substudies of TMC278-TiDP6-C209 and TMC278-TiDP6-C215 (i.e., between 1426 and 2673 ng•h/mL). While the RPV AUC_{24h} will be the primary pharmacokinetic parameter for acceptability of dose determination, the Sponsor will also consider the C_{max} and C_{0h}/C_{24h} of RPV in its determination of the acceptability of the RPV dose.

The analysis of the first 10 subjects in Cohort 2, including PK modeling and simulation to further assess the RPV pediatric dose based on accumulating data, was discussed with and endorsed by the IDMC. With this, **at the time of Amendment 10**, the following RPV dose recommendations will apply:

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

Mini-cohort data review by the Sponsor after 4 weeks of treatment on the original or adjusted dose:

If the safety and pharmacokinetic data of the first 5 subjects (mini-cohort) are acceptable i.e., the data indicate that it is likely that the desired pharmacokinetic and safety criteria for the full group of subjects with a body weight of <25 kg will be achieved (see below), then additional subjects will be enrolled to N≥12 subjects. Failure with respect to safety/tolerability and/or pharmacokinetics will result in an evaluation whether it is safe to continue the attempt to find an optimal RPV dose in children of ≥6 to <12 years of age, and if considered safe, may result in a dose adjustment.

- If none of the 5 subjects in the mini-cohort has experienced a life-threatening AE (including death) or a grade 4 AE that is at least probably related to RPV and ≤1 of the subjects has terminated the study drug due to a ≥ grade 3 at least possibly related AE, the mini-cohort has passed the safety review.
- If ≤1 of the 5 subjects in the mini-cohort has an RPV AUC_{24h} greater than the 90^{th} 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 subjects under e.g., a certain body weight is warranted.

Overall data review of subjects with body weight <25 kg by the Sponsor and IDMC after 4 weeks of treatment on the original or adjusted dose:

When reviewing the overall results, the following guidelines and stopping rules will be taken into account:

- If none of the subjects 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 subjects on this dose terminated study drug due to ≥ grade 3 at least possibly related AE, then this dose will be considered safe. If the dose is not considered safe, all relevant safety and pharmacokinetic data will be reviewed to determine whether it is safe to continue the attempt to find an optimal RPV dose in children of ≥6 to <12 years of age.

- The RPV dose will be deemed acceptable if the dose is tolerated and appears to be safe and the geometric mean RPV AUC_{24h} is between 80% and 150% of the observed geometric mean AUC_{24h} in HIV-1 infected adults from the Phase III pharmacokinetic substudies of TMC278-TiDP6-C209 and TMC278-TiDP6-C215 (i.e., between 1,426 and 2,673 ng•h/mL). For safety reasons, the individual C_{max} should be ≤440 ng/mL (1.85-fold the mean C_{max} of RPV 25 mg q.d. in healthy adults and evaluated as not posing an increased risk for QT prolongation). If an individual C_{max} is >440 ng/mL, an overall assessment of the subject's safety will be performed (including additional ECG with optional PK sample) and the RPV dose can be continued for that subject if there are no safety findings. Failure with respect to the safety and/or PK guidelines will result in an

assessment by the sponsor study team to determine whether or not a dose adjustment for the cohort may be warranted.

- If the geometric mean RPV AUC_{24h} is >150% of the observed geometric mean AUC_{24h} in adults, dose adjustment for all subjects or subjects below a certain body weight will be considered. For this, available antiviral activity/efficacy and safety results will also be taken into account.

- If the geometric mean RPV AUC_{24h} is <80% of the observed geometric mean AUC_{24h} in adults, results are not deemed satisfactory, all subjects will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to local standard of care, and Cohort 2 will be stopped.

If an adjusted RPV dose is needed, modeling and simulation will be used, incorporating all available pharmacokinetic data at that time, to propose an adjusted dose for RPV CCI [redacted] CCI [redacted] For this, available doses of RPV (based on weight-appropriate formulation which can be dosed in steps of 2.5 mg RPV) between 2.5 mg q.d. and 25 mg q.d., in increments of 2.5 mg, will be considered. The new dose scheme and clear instructions on how to handle dosing in subjects will be provided to all participating sites by the Sponsor via a written notification.

6.1.2. Discussion of Trial Design and Selection of Dose(s) in the Trial

6.1.2.1. Cohort 1: Adolescents Aged ≥12 to <18 Years

Antiretroviral therapy in ARV-naïve children provides evidence that the combination of 2 NRTIs and an NNRTI may reduce HIV RNA to undetectable levels in a substantial proportion of children[1].

Because this is the first trial with RPV (an NNRTI) to be conducted in adolescents aged ! 12 to <18 years, recruitment and analyses in this trial will be structured into 2 parts. In Part 1 (consisting of Part 1a and Part 1b), the pharmacokinetics and short-term safety and antiviral activity were to be assessed in a subgroup of adolescent patients, in order to determine the appropriateness of the RPV dose for the remainder of the adolescents. In Part 1a, an analysis was performed when the first 11 subjects (i.e., 4 subjects aged ! 12 to <15 years and 7 subjects aged ! 15 to <18 years) had been treated for 2 weeks, or discontinued earlier. These Week 2 data showed that the mean exposure in adolescents (following intensive pharmacokinetic sampling) was within 80-125% of that in adults (with mean C_{0h} ratio = 105% and mean AUC_{24h} ratio = 83%) and safety and short-term antiviral activity were satisfactory. Based on these data the IDMC agreed for these subjects to continue treatment with RPV 25 mg q.d. and their background regimen. Given the fact that the AUC ratio was at the lower end, the Sponsor decided to enroll the additional subjects in smaller cohorts and gather more intensive pharmacokinetic data in order to increase the precision of the pharmacokinetic parameter ratios,

an approach which was agreed upon with the IDMC[46]. Therefore, Part 1 of Cohort 1 was to be expanded by enrolling approximately 12 additional subjects (in order to have at least 10 evaluable subjects at Week 4) in Part 1b, aiming at an equal distribution of subjects between the two age groups (i.e., subjects ≥12 to <15 years of age and subjects ≥15 to <18 years of age). Part 1b included 14 subjects, 8 subjects in the age group ! 12 to <15 years and 6 subjects in the age group ! 15 to <18 years. This provided sufficient data on the pharmacokinetics, and short-term safety, tolerability, and antiviral effect of RPV in adolescents to assess whether continued treatment with RPV 25 mg q.d. was acceptable. The IDMC deemed the results satisfactory and hence, long-term safety, efficacy, and pharmacokinetics will be evaluated in a larger group of subjects (Part 2). It could have been that the short-term results indicated the need for a switch to a lower dose for all Part 1 subjects up to a certain body weight. In this case, prior to the start of Part 2, there could have been an additional analysis (pharmacokinetics, safety and tolerability, antiviral activity) when these subjects had been treated with the weight-adjusted dose for 4 weeks (+/-1 week). The appropriate dose for subjects entering Part 2 was assessed based on the data obtained in Part 1. The results indicated that no RPV dose adjustment was needed, as confirmed by the IDMC. For more details on the trial design, please refer to Section 2.2 and Section 6.1.1.

In Part 1a of Cohort 1, subjects with a screening viral load ≥5,000 HIV-1 RNA copies/mL could be included, an inclusion criterion which also applied in the Phase III trials. Data from these Phase III trials showed a higher virologic failure rate at Week 48 in the RPV-treated subjects with a baseline viral load >100,000 HIV-1 RNA copies/mL compared to subjects with a baseline viral load ≤100,000 HIV-1 RNA copies/mL, a trend which was also seen in the control group but to a lesser extent. Therefore, in line with the anticipated indication in adults in the European Economic Area[47], the Sponsor has decided to limit the recruitment of the adolescent population in Part 1b and Part 2 to subjects with a screening viral load ≤100,000 HIV-1 RNA copies/mL. The lower limit for screening viral load was changed as well, from 5,000 to 500 HIV-1 RNA copies/mL, as current treatment guidelines in adolescents[48] indicate that treatment initiation should primarily depend on $CD4^+$ cell count and other clinical factors, but not on viral load. So in Part 1b and Part 2, only subjects with a screening viral load ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL will be enrolled. The 4-week interim analysis of Part 1b was to be evaluated by the IDMC before the start of Part 2.

At the time of protocol amendment 6 writing, all subjects have been enrolled in Part 1 and Part 2 of this cohort. A summary of the 48-week results is provided in Section 6.1.2.2. For more details refer to the clinical study report of Cohort 1[53] or the abstract[54].

All subjects in Part 1 will continue their ART (RPV plus an investigator-selected background regimen of 2 N[t]RTIs) during the review period by the IDMC.

To ensure that the duration between baseline and the review by the IDMC for subjects in Part 1a was kept as short as possible, investigators were to identify eligible subjects in advance. Recruitment was to be started when the majority of the sites had the necessary documentation

and approvals in place and were therefore considered activated for enrollment. Recruitment for Part 1a has already been closed and the enrolled subjects can continue in the trial as judged by the IDMC. For Part 1b, recruitment could start at the individual sites as soon as the necessary documentation and approvals were in place, and was closed once the required number of subjects was recruited. Trial sites were informed in advance regarding stop of recruitment.

The 25 mg q.d. dose of RPV is the selected dose for further development in adults, based on its substantial and sustained efficacy up to 96 weeks in the Phase IIb dose-finding trial TMC278-C204, regardless of baseline viral load, and its beneficial safety profile compared to higher dosages[13], including a lack of effect on the QTc interval[20].

In adolescents, the processes that can impact the drug disposition have typically matured to adult-like activity and the pharmacokinetics in adolescents are often similar to the pharmacokinetics in adults[15]. The hepatic metabolism of RPV involves mainly CYP3A4, the activity of which has largely matured by the age of 2 years[36,37]. The adult dose of RPV (i.e. 25 mg q.d.) is therefore anticipated to result in similar exposures in adolescents as compared to adults, and to be a generally safe and efficacious dose for the adolescent population as well. This is currently confirmed in the Week 48 results of the adolescent cohort (Cohort 1).

Children with HIV infection are known to often present with a stunted growth and a low body weight compared to healthy children, even more so if additional risk factors for growth impairment are present[38]. In order to ensure that a representative fraction of the HIV-infected adolescent population can be studied in the trial, adolescents with a body weight as of 32 kg are allowed to enter the trial in Cohort 1 (i.e., the 10th percentile of the growth curve for body weight for healthy adolescents aged 12 years)[31].

In trial TMC278-C204, adult ARV treatment-naïve HIV-infected subjects weighing between 38.2 and 121.1 kg were exposed to RPV doses of 25, 75, or 150 mg q.d., and RPV was found to be generally safe and well tolerated at all doses. Furthermore, the effect of body weight on RPV exposure was found to be not significant within this population, as assessed using the population pharmacokinetic model[39]. Based on this, it is anticipated that the RPV exposure with the 25 mg q.d. dose would not be significantly different between subjects weighing 32 kg or 40 kg (40 kg being approximately the lower body weight limit observed in trial TMC278-C204). However, as the effects of body weight on exposure could become more important in the lower body weight range, the theoretical potential increase in exposure was estimated by adding body weight as a covariate function in the population pharmacokinetic model, with a widely used scaling factor for pediatrics of 0.75[14]. The RPV exposure for subjects with a body weight of 32 kg is estimated to be 16% higher for mean AUC_{24h} and 20% higher for mean C_{max}, as compared to these parameters for subjects of 40 kg. An increase in exposure of this magnitude is not expected to result in any safety issues.

A standard linear mixed model was fitted to the pooled data of the 2 thorough QT trials (TMC278-TiDP6-C131[11] and TMC278-TiDP6-C152[20]) and the pilot QT trial (TMC278-TiDP6-

C151[12]), in order to better characterize the relationship between RPV plasma concentrations and change in QTcF over a wide plasma concentration range. This indicated that at plasma concentrations of 420 ng/mL (i.e., double the C_{max} observed in HIV-infected adults on RPV 25 mg q.d.), the mean (90% CI) time-matched change from baseline in QTcF is estimated to be 4.6 ms (2.8–6.4 ms), indicating that RPV at these plasma concentrations does not cause a clinically relevant prolongation of the QTc interval.

In addition to the above, there was no pharmacokinetic/pharmacodynamic relationship for any other safety parameters in trial TMC278-C204.

Taking into account all of the above, the 25 mg q.d. dose is therefore expected to be a safe and efficacious dose for the adolescent population studied in the current trial (≥12 to <18 years with a body weight of at least 32 kg).

Also for the backbone medications ABC and 3TC used in the current trial the adult dose is recommended for children ≥30 kg, for efavirenz (approved NNRTI for pediatric use) the adult dose is recommended for children >40 kg, for AZT the adult dose is recommended for children >12 years, for FTC the adult dose is recommended for children ≥33 kg, and for TDF the adult dose is recommended for children ≥12 years and ≥35 kg.

In case of inadequate exposure, dose adjustments of RPV cannot be allowed at this stage in order to avoid exposing children to a daily dose exceeding the total adult daily dose (i.e., 25 mg q.d.).

The combined use of at least 3 active ARV drugs in ARV treatment-naïve HIV-1 infected subjects is currently recommended due to the inherent high mutation rate of HIV[1,16]. One recommended treatment regimen for ARV treatment-naïve subjects is 2 N(t)RTIs and an NNRTI. Therefore, all subjects in this trial will receive, in addition to the NNRTI RPV, an investigator-selected background regimen of 2 N(t)RTIs (AZT, ABC, or TDF in combination with 3TC or FTC). Consistent with the treatment guidelines for ART, sensitivity to the chosen N(t)RTIs should be established. In this trial, the subject's sensitivity at screening will be established using HIV-1 genotyping [1].

The combination of ABC with 3TC and AZT with 3TC are recommended and approved N(t)RTI regimens for first line use in adults and adolescents[1,16].

When looking at the subset of subjects who used AZT/3TC as background regimen in the RPV dose finding trial in adults (TMC278-C204), it was shown that there were no safety or tolerability concerns with coadministration of these NRTIs and RPV[8]. Based on the metabolic profiles and elimination, clinically relevant interactions between the other NRTI in the background regimen and RPV are unlikely[4].

For safety and efficacy information from studies using AZT, ABC, TDF, FTC, and/or 3TC or the combination products Combivir®, Truvada®, or Epzicom®/Kivexa® in combination with other ARV agents, please consult the package insert for these products.

Data from a recent clinical trial indicated that combination therapy including ABC/3TC is less effective in ARV treatment-naïve adult subjects with a high viral load at screening (≥100,000 HIV-1 RNA copies/mL) compared to regimens containing TDF/ FTC. Moreover, it was found that among adult subjects with a high viral load at screening, those subjects receiving ABC/3TC developed non-specific side effects, such as body aches, and laboratory test abnormalities, such as elevated cholesterol and triglyceride levels, faster compared to those receiving TDF/FTC[17]. Recent use of ABC was also reported to be associated with increased risk of myocardial infarction, especially in adult subjects with a high underlying cardiovascular risk[18], but this has not been confirmed by other clinical trials. Fatal hypersensitivity reactions have been associated with ART including ABC (see Section 6.5.11.3). In clinical trials, hypersensitivity reactions have been reported in approximately 5% of adult and pediatric subjects receiving ABC[18]. Since the risk for developing such reactions has been linked to the presence of the HLA-B*5701 allele[19], subjects without prior documented HLA-B*5701 negative results for whom the investigator considers ABC/3TC as background regimen should test negative for HLA-B*5701 at screening to limit the risk of hypersensitivity reactions (see Section 6.5.11.3 for details). If a subject is planned to be switched to an ABC-containing background regimen during the trial (due to intolerance, see Section 6.3.5), an HLA-B*5701 test has to be performed to determine eligibility to start ABC treatment (unless prior documented negative results are available).

There have been reports of delusions and inappropriate behavior in subjects receiving licensed NNRTIs, predominantly in subjects with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been reported in subjects receiving NVP or EFV (package insert). In trial TMC278-C204, 6.5% of subjects receiving RPV 25 mg b.i.d. were reported with depression[8]. Therefore, in order to proactively assess the risk of depression in these adolescents and children treated with RPV, at every visit indicated in the flowchart, an evaluation will be done using questionnaires or other means, as in use at the site as part of local standard of care for this population, to determine who needs to be referred for a complete mental health assessment by a mental health professional (see Section 6.4.11 for details).

Pharmacokinetic evaluations have shown that RPV is better absorbed following oral administration with food. Therefore intake should occur with a meal. For details, see Section 6.3.4. Whenever possible, RPV should be taken around the same time each day, with approximately 24 hours between the doses. Intake of the N(t)RTIs in the background regimen will be according to the locally applicable procedures and package inserts.

A trial duration of minimally 48 weeks is mandatory for providing long-term safety and efficacy data[16].

6.1.2.2. Cohort 2: Children Aged ≥6 to <12 Years

At the time of Amendment 10, 240-week results from 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[62,63] or adolescents aged ≥12 to <18 years (Cohort 1)[64,65]. Also, in the first 9 children aged ≥6 to <12 years in Cohort 2 of this study there were no emergent cortisol abnormalities and no signs or symptoms of adrenal insufficiency[66]. The following RPV dose recommendations were determined based on accumulating data and were endorsed by the IDMC, in order to achieve similar exposure to RPV compared to adults: RPV 25 mg q.d. for subjects with a body weight of ≥25 kg, and RPV 15 mg q.d. for subjects with a body weight of <25 kg. Appropriateness of these doses will be further evaluated in this study.

At the time of protocol amendment 6 writing, new clinical information has become available. For the discussion of the trial design in children (Cohort 2), a summary of relevant new and existing information has been provided below.

In mice, rats, dogs, and cynomolgus monkeys RPV affects adrenal hormone biosynthesis by direct inhibition of 21-hydroxylase and 17-hydroxylase (the latter in cynomolgus monkey only). Studies in dogs indicate that this effect does not occur after a single dose but that repeated dosing is needed to alter adrenal hormone levels in the circulation. There is potential concern for RPV to cause partial adrenal insufficiency, virilization in girls and/or growth retardation due to 21-hydroxylase inhibition. Studies in juvenile female cynomolgus monkeys, a more relevant species than dogs, did not show evidence of induction of premature ovulation, therefore the effects on the estrous cycle in dogs is not considered relevant for pre-pubertal children. In case significant inhibition of cortisol synthesis would occur (partial adrenal insufficiency), androgen production might increase. In girls, this could result in masculinization and blunted growth. In boys, due to increased levels of testosterone, growth might also be impaired. No clinically relevant mean change from baseline in serum cortisol levels or 17-hydroxyprogesterone levels over time have been observed in the clinical Phase IIb or III studies in adult men and women or in the Week 48 data of adolescents, neither for basal nor for ACTH stimulated values. In addition, growth and sexual maturation was not affected in adolescents and no clinically relevant effect was observed for gonadal laboratory parameters in adults or adolescents. As a precaution, endocrine testing will be conducted in this trial to verify whether any clinically relevant adrenal and/or gonadal effects of RPV are observed in pre-pubertal children.

Results of the Phase III studies in adults show that virologic response (<50 copies/mL, TLOVR) rates at Week 96 and in the extension after Week 96 were high and consistent between the Phase III studies. In the Week 96 pooled Phase III analysis a virologic response of <50 copies/mL (ITT, TLOVR) was achieved in 77.6% of subjects in both the RPV and control group (EFV). The proportion of virologic responders was higher in subjects with a baseline plasma viral load ≤100,000 copies/mL compared to subjects with baseline viral load >100,000 copies/mL. RPV was non inferior to control. In the Week 96 pooled Phase III analysis, beyond 48 weeks there were a limited number of additional virologic failures with fewer virologic failures in subjects with baseline viral load ≤100,000 copies/mL compared to subjects with baseline viral load >100,000 copies/mL.

In the Week 96 pooled Phase III analysis, RPV provided clear immunologic benefits. The $CD4^+$ cell count increased from Week 2 to Week 48, with a slower rate thereafter to Week 96.

In the Week 96 pooled Phase III analysis, in adult subjects treated with RPV the E138K RAM emerged most frequently and was commonly seen in combination with the M184I RAM. The FTC and 3TC RAMs M184I/V emerged more frequently in subjects experiencing virologic failure treated with RPV compared with subjects experiencing virologic failure treated with control (EFV).

In the Week 96 pooled Phase III and post Week 96 analyses, most AEs emerged in the first 48 weeks of the trial and no new safety signals were observed thereafter. Overall RPV administered at 25 mg q.d. in combination with 2N(t)RTIs was generally safe and well tolerated. The most commonly reported AEs in the RPV group were headache (15.5%), nausea (14.6%), diarrhea (13.7%), upper respiratory tract infection (12.8%), and nasopharyngitis (12.8%), with similar incidences in the control group. Dizziness and rash (preferred term) were reported statistically significantly less on RPV than on control. A lower incidence on RPV than on control was observed for treatment-related AEs (≥ grade 2), skin events of interest (including rash [grouped term]), neurologic events of interest, psychiatric events of interest, and grade 3 or 4 lipid-related laboratory abnormalities in the Week 96 pooled Phase III analysis. Small mean variations from baseline over the 96-week treatment period in adrenal and gonadal parameters indicate that neither RPV nor control had a clinically relevant inhibitory effect on 21-hydroxylase or 17-hydroxylase. There were no clinical signs or symptoms suggestive of adrenal or gonadal dysfunction. In the Week 48 and Week 96 pooled Phase III analyses, there was a gradual mean increase (from baseline) in QTcF, similar in both treatment groups at all time points. No gender difference was observed. This mean increase from baseline was less pronounced in the TDF/FTC subgroup than in the AZT/3TC subgroup. The incidence of prolonged QTcF (>480 ms) was low in both treatment groups (0.3%). There were no QTcF >500 ms, a typical pro-arrhythmic threshold. No AEs suggestive of ventricular tachyarrhythmia were reported. There was no relationship between exposure to RPV (AUC_{24h}) and the maximum mean change from baseline in QTcF across the exposure range in Phase III. No apparent relationship was observed between the pharmacokinetic parameters of RPV 25 mg q.d. and the occurrence of AEs or changes in laboratory or ECG parameters. Although it seems that RPV at the recommended dose has minimal effects on adults' ECG and no ECG-related AEs or clinically relevant ECG abnormalities were reported in the adolescent cohort of this trial (see below), its effect on the ECG parameters of children <12 years of age needs to be established and will therefore be monitored in this trial.

The Week 48 efficacy analysis results of the adolescent cohort (! 12 to <18 years of age) of this trial, demonstrated that RPV 25 mg q.d., in combination with an investigator-selected background regimen, is efficacious in adolescents of ≥12 to <18 years. A virologic response of <50 copies/mL (ITT, TLOVR) was achieved in 26/36 (72.2%) subjects at Week 48. At Week 48, the proportion of virologic responders was higher in subjects with a baseline plasma viral load ≤100,000 copies/mL (78.6%) than in the limited number of subjects with a baseline plasma viral

load >100,000 copies/mL (50%). At Week 48, 5/28 (17.9%) subjects with a baseline plasma viral load ≤100,000 copies/mL and 3/8 (37.5%) subjects with a baseline plasma viral load >100,000 copies/mL, were considered virologic failures.

RPV provided clear immunologic benefit in adolescents, as shown by an increase in $CD4^+$ cell counts over the 48-week treatment period.

Among the 5 virologic failures with baseline plasma viral load ≤100,000 copies/mL at Week 48, 3/5 (60.0%) developed RPV RAMs, which was associated with phenotypic resistance to RPV in 2/3 (66.7%) cases. These 2 subjects also carried 1 treatment-emergent NRTI RAM at the last available visit with genotypic data. The 2 other virologic failures with baseline plasma viral load ≤100,000 copies/mL did not carry treatment-emergent RPV RAMs (1 with V90I) or NRTI RAMs. Of the 3 virologic failures with baseline plasma viral load >100,000 copies/mL at Week 48, 2/3 (66.7%) developed RPV RAMs, which was associated with phenotypic resistance to RPV in both (2/2, 100.0%) cases. These 2 subjects also carried at least 1 treatment-emergent NRTI RAM at the last available visit with genotypic data. In addition, 1 virologic failure with baseline viral load >100,000 copies/mL transiently carried an RPV RAM (E138K) in the absence of NRTI RAMs, returning to wild type at trial withdrawal. The observed treatment-emergent RPV and NRTI RAMs were previously identified in the Phase III studies conducted in adults.

To date and based on all in vitro and in vivo data, 16 NNRTI RAMs when present at baseline have been identified as potential determinants of decreased antiviral activity of RPV. These NNRTI RAMs are: K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L.

The 25 mg q.d. dose in adolescents resulted in similar RPV exposure as observed in adults. No apparent relationships were observed between the RPV pharmacokinetics and efficacy or safety parameters at Week 48.

The safety data up to Week 48 demonstrated that RPV, administered at 25 mg q.d., in combination with an investigator-selected background regimen of 2 N(t)RTIs, was generally safe and well tolerated in adolescents. RPV did not appear to affect pubertal development or growth in these adolescents nor did it appear to have an effect on ECG parameters. The RPV safety profile as established in HIV-1 infected ARV treatment-naïve adults was confirmed in adolescents.

For further information on the above mentioned non-clinical and clinical data, see the Investigator's Brochure[4]. For more details about the final 48-week- and 240-week results, see the clinical study report of Cohort 1[53] or the abstract[54].

The results from the non-clinical studies and clinical trials in adults and adolescents are considered adequate to start treatment in children <12 years of age.

In the adult trials, using RPV doses of 25 mg q.d. (~0.36 mg/kg/day for a 70-kg adult), no clear effect of body weight on the RPV exposure was seen[4]. Similarly, data in adolescents between 12 and 18 years of age weighing approximately 33 to 93 kg also showed no effect of body weight on the RPV exposure[53]. While at some point, smaller body weight/size is expected to become more important and may start to have an effect on the RPV pharmacokinetics; it is at present not clear as of what age/body weight this would be. CCI [redacted] Therefore, the 25 mg qd dose is considered adequate as a starting dose for children 6 to 12 years of age. However, the pharmacokinetic data will be evaluated in real-time every time a child has completed its intensive pharmacokinetic visit, and in the event the pharmacokinetic guidelines (see Section 6.1.1.2.1) cannot be met for the mini-cohort or full group of subjects with a body weight of <25 kg, an alternative dose will be determined for evaluation. The background regimen selection will be similar as in Cohort 1 (adolescents ≥12 to <18 years of age): a regimen of 2 N(t)RTIs will be selected by the investigator. For details about timing of dosing, see Section 6.3.4.

In Cohort 2, children with a body weight as of 17 kg are allowed to enter the trial in this cohort (i.e., the 10th percentile of the growth curve for body weight for healthy children aged 6 years)[31].

Similar as in Cohort 1, the risk of depression in subjects in Cohort 2 will be assessed at every visit indicated in the flowchart (see Section 6.4.11 for details).

To accommodate regulatory requirements concerning the evaluation of RPV in the pediatric population, overall across studies C213 (Cohort 2; children aged ≥6 to <12 years) and TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥11 kg), approximately 40 subjects will be enrolled of which at least 12 subjects with a body weight of <25 kg, including at least 7 subjects with a body weight of <20 kg. The PK data from Cohort 2 will be combined with the data from pediatric study TMC278HTX2002.

The analysis of the first 10 subjects in Cohort 2, including PK modeling and simulation to further assess the RPV pediatric dose based on accumulating data, was discussed with and endorsed by the IDMC. With this, **at the time of Amendment 10**, the following RPV dose recommendations will apply to newly enrolled subjects:

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

All ongoing subjects in Cohort 2 (who are already in the post Week 48 treatment extension period **at the time of Amendment 10)** will remain on the RPV 25 mg q.d. dose + 2 N(t)RTIs (investigator-selected), until their roll-over to study TMC278IFD3004 has been completed (see addendum 7.11). All newly recruited subjects will start treatment with the weight-appropriate

RPV dose stated above + 2 N(t)RTIs (investigator-selected), until they reach a total treatment duration of 48 weeks or discontinue earlier. If newly recruited subjects with a body weight of <25 kg, increase in weight such that they require a 25 mg RPV dose, they can change to the 25 mg tablet formulation.

To further evaluate and confirm the RPV dose for subjects with lower body weight, newly enrolled subjects with a body weight of <25 kg require intensive PK evaluation. An overall analysis of the intensive pharmacokinetic data and all available safety, tolerability and antiviral activity/efficacy data will be reviewed by the Sponsor and the IDMC to assess appropriateness of the dose (see section 6.1.1.2.1 for dose evaluation criteria).

- If the results are not deemed satisfactory, and no alternative RPV dose seems feasible, all subjects will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to local standard of care, and Cohort 2 will be stopped.

- If the results are not deemed satisfactory but concerns can be addressed by adjusting the RPV dose (doses of >25 mg q.d. are not allowed) for certain subjects (e.g. up to a certain body weight), those subjects will be switched to an adjusted dose, while those that don't need dose adjustment, will continue their treatment. For all subjects who require an RPV dose adjustment, a 24-hour intensive pharmacokinetic evaluation after 14 to 18 days on the adjusted dose will be performed. After the subjects have been treated with the adjusted RPV dose for at least 4 weeks or discontinued earlier, an analysis of the intensive pharmacokinetic data (after 14 to 18 days of RPV dosing), and all available safety, tolerability and antiviral activity/efficacy data will be reviewed. If, after review of the data, the RPV dose is still not acceptable, the process will be repeated until an acceptable RPV dose is found or it is deemed necessary to stop Cohort 2.

Once an appropriate RPV dose has been selected, Part 1 of Cohort 2 will be considered complete and Part 2 in which long-term safety, efficacy, and pharmacokinetics of RPV will be evaluated, will start. For more details on the trial design, please refer to Section 2.2 and Section 6.1.1.

As in Cohort 1, a trial duration of minimally 48 weeks is mandatory for providing long-term safety, tolerability and efficacy data in this age group[16].

6.2. Trial Population

6.2.1. Sample Size

6.2.1.1. Cohort 1: Adolescents Aged ≥12 to <18 Years

Part 1a: N = 11 subjects (actual) and

Part 1b: N =14 subjects (actual)

If in Part 1, subjects discontinued the trial before receiving their first dose of study drug, additional subjects could have been recruited to have at least 10 subjects starting treatment each in Part 1a and Part 1b. If subjects were prematurely withdrawn from the trial after starting treatment for reasons other than drug tolerability/safety, additional subjects could have been recruited to aim for at least 10 evaluable subjects in each Part 1a and Part 1b at the time of intensive pharmacokinetic sampling.

Part 2: N ≥35 subjects (including all subjects already included in Part 1), regardless of dose switch.

For more details concerning the sample size, see Section 6.6.1.

6.2.1.2. Cohort 2: Children Aged ≥6 to <12 Years

As of Amendment 10 approximately 40 subjects will be enrolled in this Cohort 2 and in pediatric study TMC278HTX2002 combined: at least 12 with a body weight of <25 kg, including at least 7 with a body weight of <20 kg.

For more details concerning the sample size, see Section 6.6.1.

6.2.2. Inclusion Criteria

If there is a question about the inclusion criteria below, the investigator should consult with the appropriate Sponsor representative before enrolling a subject in the trial.

Subjects who meet all of the following criteria are eligible for this trial:

1. Cohort 1: Boys or girls, aged ≥12 to <18 years.

   Cohort 2: Boys or girls, aged ≥6 to <12 years.
2. Cohort 1: Subject's weight is ≥32 kg.

   Cohort 2: Subject's weight is ≥17 kg.
3. Subject with documented HIV-1 infection.
4. Subject willing and able to give consent. In case the subject's age is below the cut-off age for consent (according to local regulations), their parent/caregiver should be able and willing to give consent, and the subject will be informed about the trial and asked to give positive assent.

5. Subject can comply with the protocol requirements.
6. Subject has, prior to screening, never been treated with a therapeutic HIV vaccine or an HIV drug with the exception of a single dose of NVP (Cohort 1 and Cohort 2) or up to 6 weeks of AZT use (Cohort 2 only) to prevent MTCT.
7. HIV-1 plasma viral load at screening ! 500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL (assayed by RNA polymerase chain reaction [PCR] standard specimen procedure).

   Note: For Cohort 1 Part 1a, subjects with a screening viral load ≥5,000 HIV-1 RNA copies/mL were allowed.

   Note: To reassess eligibility, retesting of a screening value that leads to exclusion will be allowed only once during the screening period using an unscheduled visit.

8. In the judgment of the investigator, it is appropriate to initiate ART based on the subject's medical condition and taking into account guidelines for the treatment of HIV-1 infection in children of this age group.
9. Results from the screening HIV-1 genotype demonstrate sensitivity to the selected N(t)RTIs.
10. Subject is able to swallow the RPV tablet as a whole (since the tablet cannot be chewed, broken, or crushed), except when the appropriate RPV dose for the subjects is determined to be <25 mg (only applicable for subjects enrolled after it has been decided that a lower RPV dose is appropriate for subjects up to a certain e.g., age or body weight). In this case an age-appropriate formulation other than the tablet formulation will be provided.
11. The subject agrees (or their parents/caregivers agree, in case the subject's age is below the cut-off age for consent according to local regulations, in which case the subject is informed and asked to give positive assent) not to start ART before the baseline visit.
12. General medical condition, in the investigator's opinion, does not interfere with the assessments and the completion of the trial.

6.2.3. Exclusion Criteria

If there is a question about the exclusion criteria below, the investigator should consult with the appropriate Sponsor representative before enrolling a subject in the trial.

Subjects meeting one or more of the following criteria cannot be selected:

1. Any previous use of ARVs, with the exception of a single dose of NVP (Cohort 1 and Cohort 2) or up to 6 weeks of AZT use (Cohort 2 only) to prevent MTCT.

   Note: Cohort 1: Subjects who were infected by MTCT are allowed to enter, provided the mother was ARV treatment-naïve at the time of delivery with the exception of NVP for no more than 3 days.

2. Having documented genotypic evidence of NNRTI resistance at screening or from historical data available in the source documents, i.e., ! 1 NNRTI RAM from the following list (the list

was compiled on the basis of the list of IAS-USA NNRTI RAMs[21] 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

3. Previously documented HIV-2 infection.
4. Subject has 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 N(t)RTI in the background regimen. HLA-B*5701 testing is not required for subjects with prior documented negative results.
5. Use of disallowed concomitant therapy from 4 weeks prior to the baseline visit.
6. Any condition (including but not limited to alcohol and drug use), which, in the opinion of the investigator, could compromise the subject's safety or adherence to the protocol.
7. Life expectancy less than 6 months.
8. Subject has any currently active Acquired Immunodeficiency Syndrome (AIDS) defining illness (Category C conditions according to the Centers for Disease Control and Prevention [CDC] Classification System for HIV Infection 1993).

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

   Note: Primary or secondary prophylaxis for an AIDS-defining illness is allowed in case the medication used is not part of the disallowed medication.

9. Any active clinically significant disease (e.g., pancreatitis, cardiac dysfunction, active and significant psychiatric disorders, clinical suspicion of adrenal insufficiency, hepatic impairment) or findings during screening or medical history that, in the investigator's opinion, would compromise the outcome of the trial.
10. Subject has a known or suspected acute (primary) HIV-1 infection.
11. Any current or history of adrenal disorder.
12. Previously demonstrated clinically significant allergy or hypersensitivity to any of the components of the study drug (RPV) or the selected NRTIs. In this last case, the other N(t)RTI may be selected.
13. Receipt of any investigational drug or investigational vaccine within 90 days prior to the first administration of RPV.

14. Pregnant or breastfeeding girl.
15. Heterosexually active girls of childbearing potential without the use of effective birth control methods or not willing to continue practicing these birth control methods from screening onwards until at least 30 days after last intake of RPV.

    Note: RPV 25 mg q.d. did not change the pharmacokinetics of the oral contraceptives ethinylestradiol plus norethindrone, nor did it alter the pharmacodynamics[40].

However, to be eligible for this trial, girls of childbearing potential **must agree to use one of the following birth control methods**:

- A diaphragm or cervical cap and the male partner should use a condom;
- A hormonal contraceptive or an intra-uterine device (IUD) in combination with a barrier contraceptive (i.e., male condom, diaphragm, cervical cap, or female condom);

  or

- Be non-heterosexually active, practice sexual abstinence or have a vasectomized partner.

Note: A female condom and a male condom should not be used together as friction between the two can result in failing of either product.

Note: Spermicides should not be used as this can potentially increase the rate of HIV-1 transmission[22].

Note: A cervical cap has been shown to be less effective in parous women. Therefore, the combination of a cervical cap with oral contraceptives is preferably not used in parous girls in this trial.

16. Heterosexually active boys without the use of effective birth control methods or not willing to continue practicing these birth control methods from screening onwards until 30 days after last intake of RPV.

    Note: All HIV-infected boys are advised to use a condom to reduce the risk of transmitting HIV.

17. Any grade 3 or 4 laboratory toxicity according to the Division of AIDS (DAIDS) grading table (see Section 7.2, Addendum 2), except for:
    - Grade 3 absolute neutrophil count
    - Grade 3 platelets
    - Grade 3 glucose elevation in diabetics
    - Asymptomatic grade 3 pancreatic amylase elevation
    - Asymptomatic grade 3 triglyceride / cholesterol / glucose elevation

- Asymptomatic grade 4 triglyceride elevation

18. Subject has active tuberculosis and/or is being treated for tuberculosis at screening.

19. Subject has one or more of the following risk factors for QTc prolongation:
    - A confirmed prolongation of QT/QTc interval, e.g., repeated demonstration of QTcF (Fridericia correction) interval >450 ms in the screening ECG
    - Pathological Q-waves (defined as Q-wave >40 ms or depth >0.4-0.5 mV)
    - Evidence of ventricular pre-excitation
    - Electrocardiographic evidence of complete or incomplete left bundle branch block or complete or clinically significant incomplete right bundle branch block
    - Evidence of second or third degree heart block
    - Intraventricular conduction delay with QRS duration >120 ms (>90 ms for subjects <12 years of age).
    - Bradycardia as defined by sinus rate <50 bpm
    - Personal or family history of long QT syndrome
    - 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.
    - Syncopal episodes if repeated, unexplained, and unrelated to emotional distress.
    - Risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia, hypomagnesemia)

20. Subject enrolled in other clinical trials that include any blood sampling with a volume higher than 50 mL taken over the course of 6 months, specimen collection, or other interventional procedure. Concurrent participation in non-interventional observational trials is allowed as long as there is no impact on the objectives of this trial. Data collected in this trial can be reported in the observational trial (see also Section 6.2.4.2).

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 period (to reassess eligibility).

Note: Investigators should ensure that all trial enrollment criteria have been met at screening. If a subject's status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the trial. Section 3.4, Source Data, describes the required documentation to support meeting the enrollment criteria.

6.2.4. Precautions and Restrictions

Potential subjects must be willing and able to adhere to the following precaution measures and restrictions during the course of the trial to be eligible for participation.

6.2.4.1. Precautions

It is the investigator's responsibility to provide appropriate counseling about precautions to avoid the risk of transmitting HIV.

Since the effects of RPV on gestation are unknown, heterosexually active boys and girls of childbearing potential should receive counseling about birth control methods[23].

Boys and girls of childbearing potential having heterosexual intercourse must agree to use 2 contraceptive methods in conjunction with their sex partner, i.e., **use a condom in combination with hormonal contraceptives, an IUD, diaphragm, or cervical cap.**

Note: A female condom and a male condom should not be used together as friction between the two can result in failing of either product.

Note: Spermicide should not be used as this can potentially increase the rate of HIV-1 transmission[22].

Note: A cervical cap has been shown to be less effective in parous women. Therefore, the combination of a cervical cap with oral contraceptives is preferably not used in parous girls in this trial.

All HIV-infected boys are advised to use a condom to reduce the risk of transmitting HIV.

These precautions apply from screening onwards until one month after the last study drug administration, i.e., until 30 days after the end of the treatment period or one month after discontinuation of RPV in case of premature discontinuation.

For details on the existing data with regard to the reproductive toxicity of RPV, please see the current Investigator's Brochure[4].

Girls should not breastfeed when taking RPV, as the effects to their newborn child are unknown. Girls who have a newborn child should talk to their investigator about the best way to feed their child. They should be aware that HIV could be transmitted through breastfeeding.

For the N(t)RTI background regimen, the package insert should be consulted with regard to directions concerning birth control and breastfeeding.

6.2.4.2. Restrictions

During the conduct of the trial, subjects are not allowed to participate in any other clinical trials that include any blood sampling with a volume higher than 50 mL taken over the course of 6

months, specimen collection, or other interventional procedure. Concurrent participation in non-interventional observational trials is allowed as long as there is no impact on the objectives of this trial. Data collected in this trial can be reported in the observational trial.

No treatment interruptions are allowed prior to intensive PK in either cohort of the trial.

The consumption of grapefruit juice is not allowed during the trial. In addition, the subjects included prior to intensive PK in either cohort of the trial, may not consume beverages containing quinine (e.g., tonic, bitter lemon, bitter alcoholic beverages containing quinine), until after the pharmacokinetic sampling day at Week 2. Refer to Section 6.3.13.1 for more information on disallowed medication.

6.2.5. Removal of Subjects From Therapy or Assessment

Severe acute exacerbations of hepatitis have been reported after discontinuation of 3TC in subjects with chronic hepatitis B infection who are using this agent in their ARV regimen. Discontinuation of this agent for any reason in subjects with hepatitis B infection should be undertaken with caution. Careful clinical and laboratory assessment of the hepatic status should be undertaken for at least several months in such subjects. Initiation of specific anti-hepatitis B therapy may be required.

Subjects **may** be withdrawn from the trial if:

1. An SAE occurs.
2. They fail to comply with the protocol requirements or to cooperate with the trial staff.
3. They do not respect the washout period of disallowed medication (i.e., a period of at least 4 weeks prior to first intake of RPV), or start treatment with one of the medications reported on the list of disallowed medications (see Section 6.3.13).
4. The subject experiences a grade 3 AE or confirmed grade 3 laboratory abnormality, according to DAIDS grading table (see the DAIDS grading table in Addendum 2, Section 7.2). Exceptions are (unless clinical assessment foresees an immediate health risk to the subject):

   % Glucose elevations of grade 3 in subjects with pre-existing diabetes (see Section 6.5.11.1)

   % Asymptomatic glucose, triglyceride, or cholesterol elevations of grade 3 (see Sections 6.5.11.1 and 6.5.11.2)

   % Asymptomatic pancreatic amylase elevations of grade 3 in subjects with no history or concomitant disease of pancreatitis (see Section 6.5.4)

   % A grade 3 AE that is considered not related or doubtfully related to RPV

   For grade 3 cutaneous reaction/rash, allergic reaction, or neurological events, persistent grade 3 glucose elevations despite appropriate antidiabetic medication/treatment, grade 3 elevation in lipase, aspartate aminotransferase (AST) or alanine

aminotransferase (ALT), grade 4 elevation in pancreatic amylase, grade 3 or 4 hypomagnesemia, and grade 3 nausea and diarrhea, see must be withdrawn criteria.

Note: For grade 3 or 4 laboratory abnormalities, subjects should have a confirmatory measurement preferably within 48 hours after the laboratory results become available to the site.

5. The subject experiences an ABC hypersensitivity reaction (see Section 6.5.11.3); ABC treatment must be discontinued immediately. N(t)RTI background regimen will be replaced by an alternative regimen consisting of 2 N(t)RTIs (Brand name versions or generics with tentative US FDA approval and/or WHO prequalified drugs. If not available; generic drugs approved by the local Health Authorities or drugs procured by the UN international organizations can be allowed upon approval by the sponsor.). At all times the background regimen should consist of 2 N(t)RTIs and the subject's HIV-1 genotype at screening should show sensitivity to the alternative N(t)RTIs. The subject must never be rechallenged with any medicinal product that contains ABC (Ziagen®, Trizivir®, or Epzicom®/Kivexa®).
6. The subject demonstrates:

   % Loss of virologic response (i.e., 2 consecutive measurements of >400 HIV-1 RNA copies/mL at least 2 weeks apart after having been confirmed virologic responder [defined as having had 2 consecutive measurements of <400 HIV-1 RNA copies/mL]). Withdrawal of the subject should be based on clinical judgment and preferably be discussed with the Sponsor.

Subjects **must** be withdrawn from the trial if:

1. The pharmacokinetics or safety and antiviral activity/efficacy of RPV in the first part of either cohort of the trial are not satisfactory (as judged by the IDMC), the subjects included in this first part will be seen for a Withdrawal visit, treatment with RPV will be stopped, subjects will be switched to a locally available ARV regimen or local standard of care, and the cohort will be stopped (see also Section 6.1.1). Until the review by the IDMC has taken place, subjects will continue the intake of RPV and the background regimen.

   In case a cohort is stopped after the intensive pharmacokinetic sampling, a sample of the subjects participating in this cohort will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ARV regimen. When determination of HIV-1 genotype on this sample is not possible due to a too low viral load, the new ARV regimen will be based on the screening HIV-1 genotyping result.
2. The subject or parent/caregiver withdraws consent.
3. The investigator considers, for safety reasons, it is in the best interest of the subject that he/she be withdrawn.
4. Pregnancy has been determined.
5. The subject demonstrates:

- Lack of virologic response, defined as confirmed decrease in plasma viral load <1.0 $\log_{10}$ at Week 12 from the baseline viral load (i.e., 2 consecutive measurements at least 2 weeks apart).

  or

- Resistance development to study treatment, defined as an increase in plasma viral load of at least 0.5 $\log_{10}$ HIV-1 RNA copies/mL above the nadir and the detection of at least one NNRTI or NRTI RAM that was not present at screening and/or baseline.

Confirmation may be obtained by performing an unscheduled visit.

Note: In order to assist in the selection of a new ARV regimen after withdrawal from either cohort of the trial, HIV-1 genotyping reports from the sample at the first visit after confirmed loss of response, as long as the viral load is sufficiently high to allow HIV-1 genotyping, and from the Withdrawal visit will be provided to the investigator upon request.

Note: Subjects undergoing a controlled treatment interruption for tolerability reasons are exempted from the withdrawal criteria for virological failure up to 12 weeks after the end of the treatment interruption.

6. The subject develops tuberculosis during the trial. He/she will be withdrawn from the trial to allow appropriate tuberculosis therapy to be installed.
7. The subject experiences a grade 3 or 4 cutaneous reaction/rash (see Section 6.5.1), allergic reaction (see Section 6.5.2), or neuropsychological event (see Section 6.5.7), according to the DAIDS grading table (see Addendum 2, Section 7.2).
8. The subject experiences, after ARV medication interruption because of a confirmed grade 3 increase in ALT or AST, a confirmed recurrence of grade 3 or 4 increase in ALT or AST after restarting ARV medication (see Section 6.5.3).
9. The subject experiences a confirmed grade 3 increase in ALT or AST with a confirmed grade 3 or 4 increase in total bilirubin (see Section 6.5.3).
10. The subject experiences, after ARV medication interruption because of confirmed grade 3 or 4 elevation in lipase, a confirmed recurrence of grade 3 or 4 elevation of lipase after restarting ARV medication (see Section 6.5.4).
11. The subject experiences, after ARV medication interruption because of confirmed grade 4 elevation in pancreatic amylase, a confirmed recurrence of grade 4 elevation in pancreatic amylase after restarting ARV medication (see Section 6.5.4).
12. The subject experiences, after ARV medication interruption because of grade 3 nausea or diarrhea, a recurrence of grade 3 nausea or diarrhea, after restarting ARV medication, despite the use of antiemetics or appropriate medication, respectively (see Section 6.5.8 and 6.5.9, respectively).
13. The subject, without pre-existing diabetes, has persistent grade 3 or 4 glucose elevations despite appropriate antidiabetic medication/treatment (see Section 6.5.11.1).

14. The subject experiences a grade 4 AE or confirmed grade 4 laboratory abnormality, according to DAIDS grading table (see the DAIDS grading table in Addendum 2, Section 7.2). Exceptions are, unless clinical assessment foresees an immediate health risk to the subject:

    % Glucose elevation of grade 4 in subjects with pre-existing diabetes (see Section 6.5.11.1)

    % Asymptomatic glucose or triglyceride elevations of grade 4 (see Sections 6.5.11.1 and 6.5.11.2)

    % Confirmed pancreatic amylase and lipase elevations of grade 4 (see criterion 9) (see Section 6.5.4)

    % A grade 4 AE (except cutaneous reaction/rash, allergic reaction, or neuropsychological event) that is considered not related or doubtfully related to RPV

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

15. The subject is diagnosed with acute hepatitis A, B, or C infection after baseline.
16. The subject experiences treatment-limiting clinical hepatitis (see Section 6.5.5.2), or pancreatitis (see Section 6.5.11.6), that is judged at least possibly related to RPV.
17. The subject experiences confirmed hyperlactatemia (>2x upper limit of laboratory normal range [ULN]) that is considered at least possibly related to RPV (see Section 6.5.11.4).
18. The subject experiences a confirmed QTc prolongation:

    % QTcF ! 500 ms or a confirmed increase in QTcF from screening of ! 60 ms (if the subject is >16 years old) (see the DAIDS grading table in Addendum 2, Section 7.2);

    % QTcF ! 480 ms (if the subject is &16 years old) (see the DAIDS grading table in Addendum 2, Section 7.2).

19. Cohort 1: If the subject does not achieve a cortisol value of ≥500 nmol/L (18,1 µg/dL) on at least one of the 3 time points of cortisol measurement during the ACTH stimulation test (i.e., morning cortisol, 30 or 60 minutes after ACTH stimulation) at a trial visit where ACTH stimulation testing is done (as a result of 2 consecutive cortisol values being <248 nmol/L [9 µg/dL] or as a result of an abnormal ACTH test at baseline or Week 48) and if this subject shows clinical signs and symptoms of adrenal insufficiency (see Section 6.5.5), which are evaluated in conjunction with other possible confounding factors (e.g., concomitant medication, AEs,…), withdrawal of the subject should be discussed with the Sponsor. Appropriate clinical follow-up, including further endocrine evaluations, should be installed[24].

    Note: An unscheduled ACTH test should only be performed if the morning cortisol level is <248 nmol (9 µg/dL) at 2 consecutive measurements or if the scheduled ACTH test at baseline or Week 48 is abnormal (i.e., all cortisol values [prior to and after ACTH

stimulation] are <500 nmol/L [18.1 µg/dL]). This ACTH test can be done at the next scheduled visit as long as there are no clinical signs or symptoms or laboratory abnormalities (other than cortisol) that could indicate hypoadrenalism. The procedure of testing and confirming abnormal cortisol and measuring the ACTH-stimulated cortisol value should not exceed 16 weeks.

Cohort 2: If, after the abnormal ACTH stimulation test (i.e., the cortisol value after ACTH stimulation is <500 nmol/L [18.1 µg/dL]) at Week 24 (if applicable), the repeat ACTH stimulation test results are abnormal and if the subject shows clinical signs and symptoms of adrenal insufficiency, withdrawal of the subject should be discussed with the Sponsor. Also, if a subject shows clinical signs and symptoms of adrenal insufficiency and the unscheduled ACTH stimulation test is abnormal, withdrawal of the subject should be discussed with the Sponsor. For more details see Section 6.4.9.2.3 and 6.5.5. Appropriate clinical follow-up, including further endocrine evaluations, should be installed[24].

As of Amendment 10 the ACTH stimulation test is not scheduled on Day 1 and Week 24 but needs to be performed in case of confirmed abnormally low cortisol (<248 nmol/L [9 µg/dL]) or signs or symptoms of adrenal insufficiency (see Section 6.4.9.2.3.2). If the ACTH stimulation test is abnormal (i.e., the cortisol value after ACTH stimulation is <500 nmol/L [18.1 µg/dL]), an ACTH stimulation test must be performed at the next scheduled visit or at least within the next 8 weeks, with measurements of cortisol and 17-hydroxyprogesterone (see Section 6.4.9.2.3.2).

20. The subject experiences a grade 3 or 4 decrease in serum magnesium (see Section 6.4.9.2.2).
21. In either Cohort of the trial, the total cumulative duration of treatment interruptions for suspected toxicities is more than 8 weeks (interruptions are counted cumulatively within a time frame of 48 weeks) or the duration of a single treatment interruption for a suspected toxicity is more than 4 weeks.
22. For toxicity management of subjects reporting specific toxicities, refer to Section 6.5.

When a subject withdraws before completing the trial, the reason for withdrawal is to be documented in the electronic Case Report Form (eCRF) and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

All subjects prematurely discontinuing the trial (i.e., before Week 48), must be seen for a Withdrawal visit and a follow-up visit at 4 weeks post-treatment, except in the case of withdrawal of consent. All subjects who discontinue the trial and who have ongoing (S)AEs, laboratory abnormalities, or viral load increase at the last on-treatment visit, will also be seen for a follow-up visit. Any retest of abnormal laboratory results or plasma viral load/resistance testing should be captured in this C213 study if the subjects roll over to the TMC278IFD3004 study. Additional unscheduled visits may be performed for safety/tolerability reasons and for confirmation of plasma viral load results. For these subjects, the date and reasons for discontinuation should be completed on the Trial Termination pages of the eCRF, on the date of discontinuation. Remaining data should be completed on the date of the last scheduled follow-up visit.

If a subject is lost to follow-up, every reasonable effort must be made by the trial site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

6.3. Treatment

6.3.1. Identity of Investigational Product

The study drug, RPV, will be provided under the responsibility of the Sponsor.

RPV is formulated as an oral film-coated tablet CCI [redacted] containing 27.5 mg of RPV as the hydrochloric acid salt R314585, equivalent to 25 mg of RPV as the free base. The tablet contains lactose monohydrate.

For adjusted dosing, an age-appropriate formulation will be provided in the form of tablets containing 2.5 mg of RPV as the free base. Tablets must be dispersed prior to use.

6.3.2. Other Medication Administered in the Trial

The investigator-selected N(t)RTIs will be AZT, ABC, or TDF in combination with 3TC or FTC, whichever are approved and marketed or considered local standard of care for children aged ! 6 to <18 years in a particular country. The background regimen will be given as the co-formulation or as the separate components according to local availability and use in the country (e.g., Combivir® or AZT/3TC, Epzicom®/Kivexa® or ABC/3TC, Truvada® or TDF/FTC).

N(t)RTIs will be prescribed by the investigator and reimbursed by the Sponsor during the first 48 weeks of treatment. During the 4-year treatment extension period if applicable, it is not the Sponsor's intention to reimburse N(t)RTIs (Note: for countries where it is objectionable or impossible for N[t]RTIs to not be reimbursed during the extension period, the Sponsor will consider reimbursement of N[t]RTIs on a case by case basis).

6.3.3. Dosage and Treatment Overview Per Subject

All subjects will receive RPV in combination with an investigator-selected background regimen consisting of 2 N(t)RTIs:

Screening period (maximum 8 weeks)	No ARV treatment administration.
Initial Treatment period (48 weeks)	RPV 25 mg q.d., administered as 1 RPV tablet; or RPV adjusted dose q.d. administered as age-appropriate formulation other than the tablet formulation, if applicable; plus An investigator-selected background regimen consisting of 2 N(t)RTIs.
Treatment extension, if applicable (192 weeks)	
Follow-up period (4 weeks)	**Investigator-selected regimen.**

Subjects who started on the age-appropriate formulation, in case an adjusted RPV dose was required, will increase their RPV dose according to the final dosing schedule by weight/age

bands as they grow. If subjects increase in weight and/or age such that they require a 25-mg RPV dose, they can change to the 25-mg tablet formulation.

The selected N(t)RTIs will be used in doses that are specified in the individual product labels or for which sufficient supporting data are available for use in this age group. Only branded versions of the N(t)RTIs, or generics with tentative US FDA approval and/or WHO prequalified drugs are to be prescribed by the investigator. If not available; generic drugs approved by the local Health Authorities or drugs procured by the UN international organizations (i.e., UNICEF) can be allowed upon approval by the sponsor. Applicable procedures and guidance based on package inserts should be respected.

For those subjects who do not tolerate the selected N(t)RTIs, switching to alternative N(t)RTIs (Brand name versions or generics with tentative US FDA approval and/or WHO prequalified drugs. If not available; generic drugs approved by the local Health Authorities or drugs procured by the UN international organizations can be allowed upon approval by the sponsor.) is allowed for some predefined toxicities (see Section 6.3.5 for details).

6.3.4. Timing of Dosing

Pharmacokinetic evaluations have shown that RPV is better absorbed following oral administration with food. Therefore, RPV should always be administered with a meal.

Whenever possible, RPV should be taken around the same time each day (each dose should be separated by approximately 24 hours). The 25-mg tablets should be taken as a whole, and cannot be chewed, broken, or crushed.

Before the visit of the intensive pharmacokinetic sampling, subjects participating in the first part of either cohort of the trial should take RPV with breakfast. This breakfast will be standardized in the morning of the intensive pharmacokinetic sampling. The standardized breakfast, provided at the site for Cohort 1, will consist of four slices of bread with ham or cheese, or cold cereal (1 serving size) and 2 pieces of toast, butter, jelly, and one or two cups of orange juice, coffee or tea, with milk and/or sugar, as desired. For subjects in Cohort 2 an age-appropriate meal will be provided. If more practical, subjects can switch the intake of RPV to another time of the day (always with a meal), after the visit of the intensive pharmacokinetic sampling.

Subjects in either cohort of the trial should take RPV with the main meal of the day throughout the trial.

The intake of the N(t)RTIs in the background regimen will be according to the locally applicable procedures and package inserts, but preferably at the same time as RPV for N(t)RTIs with a q.d. regimen. For N(t)RTIs with a b.i.d. regimen, one of the doses is preferably taken together with RPV; the other dose is taken according to the label.

Subjects will be instructed to start taking their ART, respecting the food requirements, on the day of the baseline visit (Day 1), or on the following day if for some reason it is not possible to start

RPV intake at baseline. The date of the first intake of RPV will be recorded on the eCRF. All ARVs (including the background N[t]RTIs) should be started on the same day, as instructed by the investigator.

In case a subject missed the intake of RPV, and this is noticed within 12 hours of the time of usual intake, the subject should take the missed dose as soon as possible, with food. The subject may then continue his/her usual dosing schedule. In case a subject missed the intake of RPV, and it is noticed more than 12 hours after the time of usual intake, the subject should not take that dose and simply resume the usual dosing schedule. The subject should not take a double dose to make up for a missed one.

For missed doses of N(t)RTIs in the background regimen, refer to the respective package inserts.

6.3.5. Individually Selected Background Regimen

Once the screening resistance data (HIV-1 genotype) have become available, the investigator is to select a background regimen consisting of 2 N(t)RTIs, with a choice limited to AZT, ABC, or TDF in combination with 3TC or FTC, whichever is approved, marketed, or considered local standard of care for children aged ! 6 to <18 years in a particular country. The background regimen will be given as the co-formulation or as the separate components according to local availability and use in the country (e.g., Combivir® or AZT/3TC, Epzicom®/Kivexa® or ABC/3TC, Truvada® or TDF/FTC).

In clinical trials, hypersensitivity reactions have been reported in approximately 5% of adult and pediatric subjects receiving ABC[18]. Since the risk for developing such reactions has been linked to the presence of the HLA-B*5701 allele[19], subjects without prior documented HLA-B*5701 negative results in whom the investigator considers ABC/3TC as background regimen should test negative for HLA-B*5701 at screening to avoid hypersensitivity reactions (see Section 6.5.11.3 for details). If a subject is planned to be switched to an ABC-containing background regimen during the trial (due to intolerance, see paragraph below), an HLA-B*5701 test has to be performed to determine eligibility to start ABC treatment (unless prior documented specific negative results are available).

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 N(t)RTIs should be reported as AEs and should be clearly documented as leading to the change in N(t)RTIs. If the tolerability issue is related to only 1 of the 2 N(t)RTIs it is only needed to switch that one. At all times, the background regimen should consist of 2 N(t)RTIs (Brand name versions [or generics with tentative US FDA approval and/or WHO prequalified drugs]. If not available; generic drugs approved by the local Health Authorities or drugs procured by the UN international organizations can be allowed upon approval by the sponsor.), and the subject's HIV-1 genotype at screening should show sensitivity to the alternative N(t)RTIs.

Alternative N(t)RTIs will be used in doses that are specified in the individual product labels or for which sufficient supporting data are available. Only branded versions of the N(t)RTIs, or generics with tentative US FDA approval and/or WHO prequalified drugs are to be prescribed by the investigator. If not available; generic drugs approved by the local Health Authorities or drugs procured by the UN international organizations (i.e., UNICEF) can be allowed upon approval by the sponsor. Applicable procedures and treatment guidance based on package inserts of the selected N(t)RTIs should be respected.

The use of PIs, NNRTIs (other than RPV), ENF, integrase inhibitors and investigational ARVs during the trial is not allowed.

In the second part of either cohort of the trial, temporary interruption of all ARVs during the treatment period will be allowed in the event of suspected toxicity, as long as the temporary interruption is associated with and can be linked to an AE or an SAE and this is not one of the cases listed in Section 6.2.5 or Section 6.5. The maximum allowed duration of a single treatment interruption for toxicity reasons will be 4 weeks and the maximum allowed cumulative duration of the treatment interruptions for toxicity reasons will be 8 weeks (interruptions are counted cumulatively within a time frame of 48 weeks). Subjects should maintain the regular visit schedule during the treatment interruptions. Additional unscheduled visits may be performed for safety or tolerability reasons. Re-initiation of therapy including the background regimen will only be allowed once the event has resolved or decreased to a grade 2 or below. A subject must be withdrawn from the trial in case the total cumulative duration of treatment interruptions for suspected toxicities is more than 8 weeks (interruptions are counted cumulatively within a time frame of 48 weeks) or the duration of a single treatment interruption for a suspected toxicity is more than 4 weeks (see Section 6.2.5).

Special considerations may be warranted for the discontinuation of certain ARV agents:

- 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[25,26]. Some experts recommend stopping the NNRTI first, before the other ARVs (i.e., 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 subjects with hepatitis B co-infection: Severe acute exacerbations of hepatitis have been reported after discontinuation of 3TC in subjects with chronic hepatitis B infection who are using this agent in their ARV regimen. Discontinuation of this agent for any reason in subjects 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 subjects. Initiation of specific anti-hepatitis B therapy may be required (see Section 6.5.3).
- **Subjects 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 (for more details, see Section 6.5.11.3).

6.3.6. Packaging and Labeling

The study drug (RPV) will be packed under responsibility of the Sponsor.

Labels will be according to Good Manufacturing Practice (GMP)[27] Annex 13 and local requirements.

No medication can be repacked or relabeled without prior approval from the Sponsor.

6.3.7. Randomization

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

6.3.8. Blinding and Unblinding

As this is an open trial, blinding procedures are not applicable.

6.3.9. Independent Data Monitoring Committee

An IDMC will be installed to monitor pharmacokinetic, efficacy, and safety/tolerability data (including individual growth and pubertal development as part of physical examination), and to safeguard the subjects participating in this trial. The IDMC will include external experts only (two pediatric HIV specialists, a pediatric endocrinologist, a clinical pharmacologist, and a statistician). The main role of this IDMC is to evaluate accumulating pharmacokinetic, safety, and efficacy data, and to make recommendations regarding the continuation, modification, or termination of the trial.

Further details will be described in the IDMC charter.

Cohort 1: Adolescents Aged ≥12 to <18 Years

Apart from the Part 1a analysis at Week 2 (which included 11 subjects) and the Part 1b analysis at Week 4 (which includes at least 10 [evaluable] subjects), and if applicable, the analysis which includes all Part 1 subjects treated for 4 weeks (+/-1 week) with the weight-adjusted dose (See Section 6.6), another analysis has been performed when all Part 1 subjects have reached Week 12 (or discontinued earlier), a primary analysis when all subjects have reached Week 24 (or discontinued earlier), and an interim analysis when all subjects have reached Week 48 (or discontinued earlier). A final analysis will be performed when all subjects have completed the trial up to Week 240 (or discontinued earlier). The results of all analyses up to Week 48 will be shared and discussed with the IDMC.

Note: At the time of protocol amendment 6 writing, all subjects had reached Week 48 or discontinued earlier and the Week 24 and 48 analyses have been conducted.

Cohort 2: Children Aged ≥6 to <12 Years

The IDMC will be the same committee as for study TMC278HTX2002 and data from both studies can be combined. The following analyses will be shared and discussed by the IDMC:

- The analysis when a mini-cohort of 5 subjects with a body weight of <25 kg has been treated at least 4 weeks with the original and/or adjusted RPV dose.
- The analysis of overall intensive PK data when at least 12 subjects with a body weight of <25 kg, have been treated at least 4 weeks.
- The analyses when all subjects have reached 12, 24, and 48 (primary analysis) weeks of treatment.

6.3.10. Drug Accountability

The investigator, his/her designee or the hospital pharmacist must maintain an adequate record of the receipt of RPV that are provided directly by the Sponsor. Dispensation, receipt, and return, or if applicable, destruction of RPV must be documented by using the appropriate forms. All these records must be up to date and available for inspection at any time. When subjects bring their medication to the site for counting, this is not considered as a return of supplies.

6.3.11. Storage

All supplies of RPV must be stored at room temperature (15 to 30°C or 59 to 86°F) unless otherwise specified and in the original packaging.

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

- Trial number
- Reference and batch number(s)
- Kit number
- 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 site will receive notification whether the affected medication can continue to be used.

RPV must be handled strictly in accordance with the protocol and the packaging labels and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Storage and dosing instructions and an expiration date will be supplied with RPV. Unused medication and used medication packs of RPV should be returned by the subject and should be kept at the site for drug accountability purposes.

Access to RPV should be restricted to designated trial personnel.

The monitor will periodically check the supplies of RPV held by the investigator or pharmacist to ensure accountability and appropriate storage conditions of RPV.

At the end of the trial, all unused supplies of RPV will be collected by the monitor and returned to the Sponsor or will be passed over for destruction at the site (conform local regulations), or by an authorized destruction unit after authorization by the Sponsor.

For storage conditions of the N(t)RTIs used in the background regimen, consult the respective package inserts.

In case of a discontinuation of ABC for a clinically suspected hypersensitivity reaction, the subject should be asked to return all unused supplies of the ABC-containing product for disposal to prevent an accidental rechallenge.

6.3.12. Adherence

Drug adherence is critical to the success of any treatment regimen. Poor or even sub-optimal adherence to an ARV regimen can lead to incomplete suppression of viral replication and treatment failure, resulting in the emergence of drug-resistant virus.

There is evidence that adherence problems occur frequently in children. In a randomized treatment trial, caregivers reported that 30% of children missed one or more doses of ARV medications in the preceding 3 days[22]. These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to make adherence assessment, education, and support integral components of care.

To optimize adherence in this trial, counseling should be planned by the investigator/trial personnel with the subject, and their parent(s)/caregiver(s) at the screening visit to discuss the individual issues that may affect each adolescent's or child's chances of successfully adhering to treatment.

At the baseline visit, a second adherence counseling session should take place and clear instructions need to be given regarding the intake of the regimen.

A medication adherence check (e.g., review the adherence questionnaire or drug accountability) and additional medication adherence counseling should take place at every subsequent trial visit.

During the entire trial (i.e., in both parts of all cohorts of the trial), compliance to RPV and the background regimen will be assessed by the Study Adherence Questionnaire for Children and Teenagers or the Adherence Questionnaire for Caregivers (see Addenda 7 and 8) and for RPV as documented on the drug accountability form. Site staff, such as a counselor, should support the subject or their parent(s)/caregiver(s) to complete the questionnaire together, where the subject or their parent(s)/caregiver(s) provides the responses to the counselor. Once the subject or their parent(s)/caregiver(s) have completed the questionnaire, the site staff should review it for completeness. The questionnaire will be collected and the data will be entered into the trial database by the data manager.

In addition, from the start of RPV treatment until the day of intensive pharmacokinetic sampling, subjects or their parent(s)/caregiver(s) should complete a diary documenting the intakes of RPV from the start of treatment with RPV 25 mg q.d. (or adjusted dose if applicable) until the day of intensive pharmacokinetic sampling. For intakes of RPV and accompanying meals at home, subjects or their parent(s)/caregiver(s) should be asked to note the exact times of medication intakes and accompanying meals (stop times). The investigator or trial personnel should review the recorded data in the subject's diary. The diaries should be provided to data management and entered into the trial database by the data manager. In Cohort 2, subjects or their parent(s)/caregiver(s) will also be contacted via telephone or email to assess adherence (to study drug and other ARVs) and to reinforce trial instructions every day for 3 days prior to the intensive pharmacokinetic visit. If the subject has missed a dose of RPV within 10 days prior to the intensive pharmacokinetic visit, the visit should be rescheduled so as to allow steady-state of RPV to be reached.

The subjects or their parent(s)/caregiver(s) will be requested to bring unused medication and empty packaging to the unit at each visit. If a subject's medication intake is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

6.3.13. Prior and Concomitant Therapy

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the trial and different from RPV or the background N(t)RTIs, must be

documented in the Concomitant Therapy section of the eCRF. Reported information will include a description of the type of the drug, treatment period, dosing regimen, route of administration and its indication. Any change in dosage of the non-ARV medication must also be reported in the Concomitant Therapy eCRF section. Data on concomitant medication will be collected up to the last follow-up visit, even after withdrawal of a subject.

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

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 on the AE/HIV-related event section of the eCRF.

Heterosexually active boys and girls of childbearing potential must use birth control methods as outlined above in Section 6.2.4 and must be willing to continue practicing these birth control methods throughout the trial and for at least 30 days after the last intake of RPV. The use of oral, injectable, and implantable hormonal contraceptives is to be recorded in the Concomitant Therapy eCRF section.

6.3.13.1. Disallowed Concomitant Medication

For coadministered comedication, the prescribing information should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected in order to prevent any potentially serious and/or life-threatening drug interactions.

- **The following medications are not allowed from 4 weeks prior to the baseline visit until the end of treatment/Withdrawal visit:**
  - All investigational drugs
  - Drugs that can potentiate the activity of ARV drugs 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 AZT/3TC, ABC/3TC, or TDF/FTC. For any alternative N(t)RTIs in the background regimen, the respective package inserts should be consulted for concomitant use with other medications and for contraindicated medications or medications that are not recommended for concomitant use
- Subjects who discontinue their ketoconazole treatment at least 4 weeks prior to the baseline visit can be included in the trial.
- Subjects in Cohort 1 who start ketoconazole treatment during the trial need to have an ACTH stimulation test performed 2 weeks into ketoconazole treatment. If all cortisol values (prior to and after ACTH stimulation) are <500 nmol/L (18.1 µg/dL), and this subject has clinical signs or symptoms of adrenal insufficiency (see Section 6.5.5), which are evaluated

in conjunction with other possible confounding factors (e.g., concomitant medication, AEs,…), the subject should be withdrawn from the trial after discussion with the Sponsor. In addition, for subjects in either cohort of the trial who start azole treatment during this trial, additional safety monitoring as specified below is required.

- During either cohort of the trial (i.e., until after the intensive pharmacokinetic sampling), all medications labeled as having a CYP3A4 inhibitory effect are disallowed. During the rest of the trial, all medications labeled as having a CYP3A4 inhibitory effect should be used with caution. Coadministration with these agents may result in increased RPV plasma concentrations. Alternative medications without CYP3A4 inhibitory effect should always be considered as the preferred option. In case there is no alternative, additional safety monitoring is required for subjects receiving CYP3A4 inhibitory comedications for >2 days. Additional safety monitoring is also required for subjects receiving medications associated with a risk of Torsade de Pointes for >2 days[28]. 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 intake of RPV. Also, a pharmacokinetic sample needs to be drawn within 10 minutes after this ECG. The time and date of sampling and last intake of RPV should be captured in the eCRF. If the subjects experience a QTcF ! 480 ms (subjects &16 years old) or ! 500 ms (subjects >16 years old) that is confirmed by another ECG (repeat ECG should be performed within 48 hours after the site has received the abnormal result), or a confirmed increase in QTcF from baseline of ! 60 ms (only applicable for subjects >16 years old), 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 subject should be withdrawn from the trial. Approximately 1 week after withdrawal, another ECG should be performed during an unscheduled visit to ensure normalization. Refer to Table 1 for specific examples of comedications that require additional safety monitoring. In addition, grapefruit and grapefruit juice are disallowed during the whole trial in either cohort, given its CYP3A4 inhibitory effect.
- All medications labeled as having a potent CYP3A4 inducing effect are disallowed. Coadministration of RPV with these agents may result in decreased RPV plasma concentrations and potential loss of therapeutic effect. Refer to Table 1 for specific examples.
- **The following medications are not allowed from baseline onwards:** Any anti-HIV therapy other than RPV and the underlying N(t)RTIs.
- No vaccines can be given **within 4 weeks prior to baseline, and thereafter within 4 weeks preceding a viral load measurement**. Approved vaccines are allowed from Week 4 onwards as long as they are given after the sample for plasma viral load measurement is taken (if applicable). For an overview of childhood immunizations, see Addendum 10: Childhood Immunizations.
- In Cohort 2, use of systemic chronic steroids **within 30 days prior to baseline and during the trial** is disallowed. Use of both chronic inhaled and intranasal steroids within 30 days prior to ACTH stimulation testing is disallowed. Use of either inhaled or intranasal steroids is allowed during the trial.

- H_2 receptor antagonists (examples include, Pepcid, Zantac, and Axid) should only be administered **either at least 12 hours before or at least 4 hours after** RPV administration.
- Antacids should only be administered **either at least 2 hours before or at least 4 hours after** RPV administration.

For details on drug interactions with RPV and specific disallowed medication, please consult Table 1.

For contraindicated medications or medications that are not recommended for concomitant use with the background regimen, the package inserts of the background N(t)RTIs should be consulted.

Table 1: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV

Drug Class	Interaction Effect	Clinical Comment
● Antiarrhythmics		
- Bepridil	Data on interaction with RPV currently not available.	**Disallowed**. Potential for cardiac arrhythmias.
- Flecainide, propafenone, systemic lidocaine, mexilitine	Data on interaction with RPV currently not available.	**Use with caution**. Plasma concentrations of these medications may be affected when coadministered with RPV, and potential for cardiac arrhythmias. Additional safety monitoring is required if taken for >2 days[a].
- Quinidine, disopyramide, amiodarone	Data on interaction with RPV currently not available.	**Use with caution**. Plasma concentrations of these medications may be affected when coadministered with RPV, and potential for cardiac arrhythmias. Additional safety monitoring is required if taken for >2 days[a].
- Dofetilide, ibutilide, procainamide, sotalol	Data on interaction with RPV currently not available.	**Use with caution**. Potential for cardiac arrhythmias. Additional safety monitoring is required if taken for >2 days[a].
● Anticoagulants		
- Warfarin, phenprocoumon, and acenocoumarol	Data on interaction with RPV currently not available.	**Use with caution**. Plasma concentrations of these medications may be affected when coadministered with RPV. Careful monitoring of the coagulation parameters is warranted.
● 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.
● Antihyperlipidemic agents		
- Probucol	Data on interaction with RPV currently not available.	**Use with caution**. Potential for cardiac arrhythmias. Additional safety monitoring is required if taken for >2 days[a].

Table 1: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV, Cont'd

Drug Class	Interaction Effect	Clinical Comment
● Calcium channel blockers		
- Felodipine, nifedipine, nicardipine, amlodipine	Data on interaction with RPV currently not available.	**Use with caution**. Plasma concentration of these medications may be reduced when coadministered with RPV.
- Verapamil, diltiazem	Data on interaction with RPV currently not available.	**Disallowed prior to intensive PK. If no intensive PK, use with caution** Plasma concentrations of RPV may be increased and/or plasma concentrations of these medications may be decreased when coadministered. Additional safety monitoring is required if taken for >2 days[a].
● Azole antifungal agents		
- Ketoconazole, itraconazole, voriconazole Note: fluconazole is preferred option	Ketoconazole increased the exposure to RPV by 50% for AUC and by 30% for C_{max}.	**Disallowed prior to intensive PK. If no intensive PK, use with caution.** Plasma concentrations of RPV may be increased by coadministration of these medications. Additional safety monitoring is required[a] when ketoconazole, itraconazole or voriconazole are coadministered with RPV for >2 days. 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[a] for fluconazole coadministration when used in doses of 400-800 mg/day for >2 days.

Table 1: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV, Cont'd

Drug Class	Interaction Effect	Clinical Comment
● Antibiotics		
- Clarithromycin, erythromycin, roxithromycin Note: azithromycin is preferred option	Data on interaction with RPV currently not available.	**Disallowed prior to intensive PK. If no intensive PK, use with caution**. Plasma concentrations of RPV may be increased and/or plasma concentrations of these medications may be reduced when coadministered. Additional safety monitoring is required if taken for >2 days[a]. Clarithromycin and erythromycin have been associated with a risk for cardiac arrhythmias. 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.
- Rifabutin, rifampin, rifapentine	Rifabutin reduced exposure (AUC) to RPV by 46%. Rifampin reduced exposure (AUC) to RPV by 80%. No data available on interaction with rifapentine.	**Disallowed**. Coadministration may result in reduced RPV plasma concentrations an in loss of therapeutic effect.
- Telithromycin, troleandomycin	Data on interaction with RPV currently not available.	**Disallowed**. Coadministration may result in increased RPV plasma concentrations.
- Sparfloxacin, pentamidine	Data on interaction with RPV currently not available.	**Use with caution**. Potential for cardiac arrythmias. Additional safety monitoring is required if taken for >2 days[a].
● Antimalaria agents		
- Chloroquine, halofantrine	Data on interaction with RPV currently not available.	**Use with caution**. Potential for cardiac arrythmias. Additional safety monitoring is required if taken for >2 days[a].
● Glucocorticoids		
- Dexamethasone	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. *Note: In Cohort 2 use of both chronic inhaled and intranasal dexamethasone within 30 days prior to ACTH stimulation testing is disallowed. Occasional use of either inhaled or intranasal steroids is allowed.

Table 1: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV, Cont'd

Drug Class	Interaction Effect	Clinical Comment
- Other glucocorticoids	Data on interaction with RPV currently not available.	**Disallowed**. (only topical and inhalation products allowed*). Could suppress adrenal gland function. *Note: In Cohort 2 use of both chronic inhaled and intranasal steroids within 30 days prior to ACTH stimulation testing is disallowed. 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		
- e.g., 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 intake of RPV.
- Antacids (e.g. aluminum/magnesium hydroxide)	Data on interaction with RPV currently not available.	**Use with caution.** Antacids should be taken at least 2 hours before or 4 hours after intake of RPV.
● Immunomodulators		
- Cyclosporine, rapamycin, tacrolimus, sirolimus	Data on interaction with RPV currently not available.	**Use with caution**. Plasma concentrations of these medications may be affected when coadministered with RPV.
- Thalidomide	Data on interaction with RPV currently not available.	**Use with caution.** Thalidomide is not metabolized by CYPs and a pharmacokinetic interaction is not likely.
● Arsenic trioxide	Data on interaction with RPV currently not available.	**Use with caution.** Potential for cardiac arrythmias. Additional safety monitoring is required if taken for >2 days[a].

Table 1: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV, Cont'd

Drug Class	Interaction Effect	Clinical Comment
● **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 TMC278. No dose adjustments are required. Monitor for signs and symptoms of methadone withdrawal; some subjects may need an increase in the methadone dose. Methadone has been associated with a risk for cardiac arrythmias. Additional safety monitoring is required if taken for >2 days[a].
● **Levomethadyl**	Data on interaction with RPV currently not available.	**Use with caution**. Potential for cardiac arrythmias. Additional safety monitoring is required if taken for >2 days[a].
● **Antihistamines**		
- Astemizole, terfenadine	Data on interaction with RPV currently not available.	**Disallowed.** Severe cardiac arrhythmias have been reported with astemizole and terfenadine.
● **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.
● **Gastroprokinetic**		
- Cisapride	Data on interaction with RPV currently not available.	**Disallowed.** Severe cardiac arrythmias have been reported with cisapride.
● **Antiemetics**		
- Aprepitant	Data on interaction with RPV currently not available.	**Disallowed prior to intensive PK. If no intensive PK, use with caution.** Coadministration may result in increased plasma concentrations of RPV and/or decreased plasma concentrations of aprepitant. Additional safety monitoring is required if taken for >2 days[a].
- Domperidone	Data on interaction with RPV currently not available.	**Use with caution**. Potential for cardiac arrythmias. Additional safety monitoring is required if taken for >2 days[a].

Table 1: Established and Theoretical Drug Interactions With Commonly Used Comedications and RPV, Cont'd

Drug Class	Interaction Effect	Clinical Comment
● Antipsychotics, antidyskinetics		
- Pimozide	Data on interaction with RPV currently not available.	**Disallowed**. Severe cardiac arrythmias have been reported with pimozide.
- Chlorpromazine, haloperidol, mesoridazine, thioridazine, droperidol	Data on interaction with RPV currently not available.	**Use with caution**. Potential for cardiac arrythmias. Additional safety monitoring is required if taken for >2 days[a].
● 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].
● Ergot derivatives		
- dihydroergotamine, ergonovine, ergometrine, ergotamine, methylergonovine	Data on interaction with RPV currently not available.	**Use with caution.** Plasma concentrations of these medications may be affected when coadministered with RPV.

[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 the intake of RPV. Also, a pharmacokinetic sample needs to be drawn within 10 minutes after this ECG. The date and time of sampling and last intake of RPV prior to pharmacokinetic sampling should be recorded on the eCRF. If the subjects experience a QTcF ! 480 ms (subjects &16 years old) or ! 500 ms (subjects >16 years old) that is confirmed by another ECG (repeat ECG should be performed within 48 hours after the site has received the abnormal result), or a confirmed increase in QTcF from baseline of ! 60 ms (only applicable for subjects >16 years old), 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 subject should be withdrawn from the trial. 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.

6.3.13.2. Disallowed Antiretroviral Medication

The following ARVs are not allowed from baseline until the end of treatment/Withdrawal visit:

- Any investigational ARVs (except for AZT/3TC and/or ABC/3TC and/or TDF/FTC, if not registered in the participating country)
- Any PIs
- Any fusion inhibitor
- Any NNRTIs, except for RPV
- N(t)RTIs other than AZT, 3TC, ABC, FTC and TDF (unless after switch due to predefined toxicities)
- Any CCR5 inhibitors

- Any integrase inhibitor
- Any generic drugs not tentatively approved by US FDA, not prequalified by world health organizations, not approved by local health authorities or not procured by UN international organizations (eg, UNICEF).

6.4. Assessments

6.4.1. Timing of Assessments

The exact timing of the assessments is presented in the flowchart (see Section 2).

During the screening period it is allowed to assess the viral load and $CD4^+$ cell count before continuing with the other screening assessments. In such case, after obtaining informed consent, samples will be taken for determination of plasma viral load and $CD4^+$ cell count. If plasma viral load results meet the inclusion criteria and the investigator considers initiation of ART appropriate (taking into account current treatment guidelines, including $CD4^+$ cell count and the subject's clinical situation), the subject will return to the site within 2 weeks after availability of the results, for the remainder of the screening procedures. If plasma viral load results do not meet the inclusion criteria, the subject will be considered a screen failure. This way unnecessary blood draws and assessments may be avoided in a lot of subjects since screening viral load being outside the limits for inclusion is the major reason for screen failure (i.e., 33% of all screen failures in Part 1a). Within 4 weeks after the screening visit, the site should have received all data to determine the subject's eligibility.

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 assessment, if these were assessed separately before continuing with the other screening assessments), but in case of unforeseeable circumstances the screening period can be prolonged by 2 weeks maximum, resulting in a maximum screening period duration of 8 weeks.

RPV will be initiated at baseline (Day 1). Thereafter, subjects will return for visits at Week 1, Week 2, Week 4, then every 4 weeks until Week 16, every 8 weeks until Week 48, and if applicable every 3 months until Week 240.

Unscheduled visits should be planned:

- To perform a confirmatory plasma viral load determination during the treatment period in the event of suspected virologic failure (see Section 6.2.5). For Cohort 2, during this unscheduled visit, also samples for pharmacokinetics will be taken.

  Note: The minimal time between 2 consecutive plasma viral load determination measurements must be at least 2 weeks.
- To repeat PK samples if needed (see Section 6.4.8).
- To assess, confirm, and follow-up on clinically relevant AEs or laboratory abnormalities.

Note: In case a grade 3 or grade 4 laboratory abnormality occurs, a confirmatory retest should be performed by a local or central laboratory, preferably within 48 hours after receipt of the abnormal result by the site.

- To assess and ensure appropriate follow-up on cutaneous reaction/rashes (see Section 6.5.1).
- To assess and ensure appropriate follow-up on clinically suspected hypersensitivity reactions (see Section 6.5.11.3).
- To perform additional safety monitoring in case certain concomitant medications are started (see Section 6.3.13.1).
- To assess and ensure appropriate follow-up on abnormal basal or ACTH stimulated cortisol values and to perform an unscheduled ACTH stimulation test in case of clinical signs and symptoms or laboratory abnormalities (other than cortisol) indicative of adrenal insufficiency (see Section 6.4.9.2.3 and 6.5.5).
- To assess, confirm, and follow-up on abnormal QTc values on ECG (see Section 6.2.5).
- To switch subjects to an adjusted dose of RPV (dose switch visit), and to re-evaluate this dose (post switch visit[s]). The dose switch visit has to be performed as soon as possible after communication of the recommended adjusted dose.

Findings during these unscheduled visits need to be reported on designated sections of the eCRF.

Blood samples for biochemistry testing are to be taken under fasted conditions. See flowchart in Section 2 for the exact timing of these assessments.

6.4.2. Time Windows

All study visits should be scheduled relative to the baseline visit date (eg, Day 1 + 7 days for Week 1). The following time windows are recommended:

- For the Week 1 visit: ± 2 days
- For the Week 2 visit (including Week 2 post switch): ± 2 days (Cohort 1); between Day 14 and 18 (Cohort 2)
- For the Week 4 (including Week 4 post switch), Week 8, Week 12, Week 16, Week 24, Week 32, Week 40, and Week 48 visits, and the post Week 48 treatment extension visits, if applicable: ± 1 week
- Follow-up visit: 4 weeks ± 4 days after the Final/Withdrawal visit

If applicable, if the dose switch visit is done within 1 week of the next scheduled visit as indicated in the flowchart, this next planned visit can be cancelled but assessments of that visit will have to be performed at the dose switch visit. If the post switch visit is done within 1 week of the next planned visit as indicated in the flowchart, this next planned visit can be deleted but assessments of that visit that are not planned in the post switch visit will have to be added.

The timing of visits from Week 1 to Week 48 (or to Week 240 if applicable) should be based on the start date of RPV intake (which should coincide with the date of the baseline visit or the

following day if for some reason it is not possible to start intake of RPV at baseline). Some flexibility in the planning of the visits is allowed (as indicated above); however, the initial treatment duration should be 48 weeks, and the extension period, if applicable, 192 weeks. If the subject cannot return within these time windows, it might be necessary to dispense extra ARV medication to avoid a situation where the subject runs out of medication.

6.4.3. Handling of Biological Samples

All samples will be collected and processed according to the central laboratory manual. Handling and shipment of the samples and the materials will also be described in the manual. The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

The sample tubes must be labeled as described in the laboratory manual.

Samples that remain after protocol-specific assessments have been performed, may be used for further exploratory work. This exploratory work can include pharmacokinetics, metabolites, proteins, plasma protein binding, biochemistry, virus characterization, characterization of hepatitis C virus (HCV) (if applicable), and characterization of viral drug resistance, and immunologic parameters.

Apart from HLA-B*5701 testing in subjects without prior documented HLA-B*5701 negative results in whom the investigator considers ABC/3TC as the background regimen, no genomic testing will be done. All genetic samples will be destroyed after analysis.

6.4.4. Initial Subject and Disease Characteristics

At the screening visit, after signing the ICF, the overall eligibility of the subject to participate in the trial will be assessed. The subject's demographics, smoking habits, clinically relevant medical and surgical history, or pre-existing conditions (active or non active) that may be expected to impact the subject’s clinical outcome during participation in this trial (e.g., diabetes, dyslipidemia, hypertension, liver disease, neoplasms, opportunistic infections, rash, allergic reactions, etc.) and all concomitant medication will be recorded. A comprehensive physical examination including all body parts (and specifically assessment of hyperpigmentation and hirsutism) will be performed and urine and blood samples will be collected for urinalysis, biochemistry, hematology, immunology, viral pheno-and genotype, and plasma viral load determinations. Vital signs and ECG will be recorded.

Since ABC has been associated with severe hypersensitivity reactions, and the risk for developing such reactions has been linked to the presence of the HLA-B*5701 allele, subjects without prior documented HLA-B*5701 negative results in whom the investigator considers using ABC as the background regimen should test negative for HLA-B*5701 at screening (see Section 6.5.11.3 for details).

A serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed at other visits for girls who have had their first menses only, i.e., girls of childbearing potential.

At screening, it will be assessed whether girls already have had their first menses.

Height and weight will be recorded at the visits specified in the flowchart (see Section 2).

In addition, at screening, contraceptive and adherence counseling is done.

6.4.5. Antiviral Activity

At the time points specified in the flowchart (see Section 2), samples for the determination of efficacy will be taken.

Plasma viral load levels will be determined using a Roche HIV-1 viral load assay. Specimen preparation procedures are defined in the laboratory manual. Selected samples can also be tested using a 5-copy viral load test, for the purpose of exploratory analyses.

Changes in viral load, including rebound and incomplete virologic suppression, will be part of the efficacy analysis and should not be reported as AE/SAEs.

6.4.6. Immunologic Change

At the time points specified in the flowchart (see Section 2), samples for the determination of the $CD4^+$ cells (absolute and %) will be taken.

Changes in $CD4^+$ cells, either increases or decreases, will be part of the efficacy analysis and should not be reported as AE/SAEs.

6.4.7. Resistance Determinations

At time points specified in the flowchart (see Section 2), samples for the determination of viral phenotype and genotype will be taken. Viral phenotypic and genotypic determinations will be performed centrally by a qualified provider.

Note: An HIV-1 phenotyping and/or genotyping report will only be generated when the viral load is sufficiently high.

Samples collected at screening will be tested in real time for the determination of the HIV-1 genotype. Samples collected at baseline, at suspected virologic failure, at the Week 48 visit, and at the Final/Withdrawal visit will be tested for the determination of the HIV-1 genotype and phenotype, as long as the viral load is sufficiently high to allow HIV-1 genotyping and phenotyping.

Samples collected at other intervals may be selected for determination of the HIV-1 genotype and/or phenotype by the Protocol Virologist based on plasma viral load.

In case of discontinuation, the subject's new ARV regimen will be based on the results of the Withdrawal HIV-1 genotype. In case the trial is stopped after intensive pharmacokinetic sampling in either cohort, a sample of the subjects participating in this part will be analyzed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ARV regimen. When HIV-1 genotype determination on this sample is not possible, the new ARV regimen can be based on the screening HIV-1 genotyping result.

The results of the viral phenotypes and genotypes will be evaluated by the Protocol Virologist. Relevant changes in the viral phenotype and genotype, detected by the phenotyping and HIV-1 genotyping will be evaluated. These changes in viral phenotype and genotype will not be regarded as AEs.

In addition, a PBMC sample will be taken at screening and Week 48 to retrospectively characterize archived viral resistance. No human DNA analysis will be performed on these samples. Deep sequencing may be performed, considering the amounts of plasma available after standard resistance testing.

6.4.8. Pharmacokinetic Evaluations

6.4.8.1. Sample Collection and Handling

At the time points specified in the flowchart (see Section 2), blood samples will be taken to determine the RPV plasma concentrations. Samples for bioanalysis should be protected from light during sample processing and storage.

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

Cohort 1: Adolescents Aged ≥12 to <18 Years:

Only in the subjects included in the first part of Cohort 1 (Part 1), intensive pharmacokinetic sampling was to be performed during a 24-hour dosing interval at the Week 2 visit (for Part 1a subjects) and at the Week 4 visit (for Part 1b subjects) to evaluate the steady-state pharmacokinetic parameters of RPV (see Section 2.1.2 for details). Plasma samples for RPV of the subjects in the first part of Cohort 1 (Part 1) were to be divided over 2 tubes. One sample was to be used for bioanalysis of RPV (main sample) and one sample is the back-up sample. The main sample had to contain at least 500 µL of plasma.

In all subjects, sparse pharmacokinetic sampling will be performed for population pharmacokinetic analysis. A pharmacokinetic sample will be taken at all time points indicated in the flowchart (see Section 2).

When additional safety monitoring ECGs are performed, one pharmacokinetic sample should be taken within 10 minutes after each of these ECGs in order to assess the impact of the comedication on the plasma levels of RPV and to evaluate the RPV concentration-safety relationship.

Exact date and time of blood sampling and last intake of RPV will be recorded in the eCRF.

Cohort 2: Children Aged ≥6 to <12 Years

For subjects with a body weight of <25 kg, intensive pharmacokinetic sampling will be performed during a 24-hour dosing interval at the Week 2 visit (between Day 14-18) and at the 2-weeks Post Switch visit, if applicable to evaluate the steady-state pharmacokinetic parameters of RPV (see Section 2.1.2 for details).

Note: Subject or their parent(s)/caregiver(s) contact via telephone or email should take place to assess adherence (to study drug and other ARVs) and to reinforce trial instructions every day for 3 days prior to the intensive pharmacokinetic visit. If the subject has missed a dose of RPV within 10 days prior to the intensive pharmacokinetic visit, the visit should be rescheduled so as to allow steady-state of RPV to be reached.

In all subjects sparse pharmacokinetic sampling will be performed for population pharmacokinetic analysis. For more details about the sampling times, see the flowchart (Section 2).

When additional safety monitoring ECGs are performed, a pharmacokinetic sample should be taken as specified in Section 6.3.13.1.

For all pharmacokinetic samples exact date and time of blood sampling and last intake of RPV prior to this sample will be recorded in the eCRF.

6.4.8.2. Bioanalysis

Plasma concentrations of RPV will be analyzed under the responsibility of the Sponsor, using a validated analytical method.

Plasma concentrations of the N(t)RTIs can be determined (using the RPV plasma sample) by a validated analytical method, if the Sponsor decides to perform this analysis.

The bioanalysis of RPV can be performed in batches.

Results of the bioanalysis of RPV and other ARVs, as applicable, will not be made available to the investigator on real time basis, but will be included in the final study report.

6.4.9. Safety Evaluations

6.4.9.1. Adverse Events/HIV-Related Events

At each visit, the subject will be asked about any untoward medical occurrences and these will be recorded as AEs from the signing of ICF onwards. HIV-related events and the occurrence of AIDS-defining illnesses will also be recorded. For detailed definitions and reporting procedures of AEs see AEs/HIV-Related Events (Part II, Section 1).

6.4.9.2. Clinical Laboratory Tests

At the time points specified in the flowchart (see Section 2), samples for laboratory safety testing will be taken. The laboratory reports generated by the central laboratory will need to be interpreted for clinical significance, signed and dated by the investigator after which they need to be filed in the subject's medical record. In case clinically relevant changes are observed from the signing of ICF onwards, these should be reported as AEs in the AE/HIV-Related Event section of the eCRF.

The central laboratory will send the investigator an alert form whenever a grade 3 or 4 laboratory abnormality (see Addendum 2: DAIDS Table) has been observed.

In case a grade 3 or grade 4 laboratory abnormality occurs, a confirmatory retest should be performed by a local or central laboratory, preferably within 48 hours after receipt of the abnormal result by the site.

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

- asymptomatic grade 3 or 4 glucose elevations in subjects with pre-existing diabetes;
- asymptomatic grade 3 or 4 glucose or triglyceride elevations, or asymptomatic grade 3 cholesterol elevations;
- asymptomatic grade 3 pancreatic amylase elevations in subjects with no history or concomitant disease of pancreatitis.

6.4.9.2.1. Hematology

At the time points specified in the flowchart (see Section 2), blood samples for these tests will be drawn.

Hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), red blood cell (RBC) count, white blood cell (WBC) count, WBC differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count will be assessed.

6.4.9.2.2. Biochemistry

Subjects must fast overnight prior to having blood samples drawn for these tests (see flowchart, Section 2). Samples that were taken under non-fasted 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 subject has fasted overnight

Total protein, alkaline phosphatase (ALP), AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin, urea, uric acid, creatinine, electrolytes (sodium, potassium, phosphate, chloride, calcium, calcium corrected for albumin, magnesium), human serum albumin, triglycerides, pancreatic amylase, lipase, total cholesterol, high-density lipoprotein (HDL), low density lipoprotein (LDL), glucose, and insulin will be assessed.

The central laboratory will calculate the estimated glomerular filtration rate (eGFR) according to the following formula[29]:

$$\text{eGFR} = \frac{k * L\ (\text{cm})}{\text{Plasma creatinine } (P_{cr})\ (\text{mg/dL})}$$

k = 0.55 in adolescent girls aged 13-21 years, and 0.70 in adolescent boys aged 13-21 years and 0.55 in children aged 2-12 years.

If the subject is >21 years of age, the Modification of Diet in Renal Disease (MDRD) eGFR equation will be used.[58]

Lactate will be assessed in case of suspicion of lactic acidosis syndrome (see Section 6.5.11.4) and creatine phosphokinase will be assessed in case of suspicion of rhabdomyolysis. These assessments will be done at the local laboratory.

For girls of childbearing potential, the samples for biochemistry taken at screening will include a serum pregnancy test.

Additional tests may be performed at the central laboratory, if needed. However, additional testing requires approval of the Sponsor.

For more details, please see the central laboratory manual.

6.4.9.2.3. Endocrine Assessments

6.4.9.2.3.1. Cohort 1: Adolescents Aged ≥12 to <18 Years

At time points specified in the flowchart (see Section 2) an ACTH stimulation test will be done for all subjects including measurements of cortisol, 17-hydroxyprogesterone, aldosterone. After a sample for the determination of these endocrine parameters has been drawn (T_0), 250 µg of tetracosactide or cosyntropin is injected intravenously over 2 minutes or intramuscularly and additional blood samples collected 30 and 60 minutes after injection for the determination of cortisol, 17-hydroxyprogesterone and aldosterone. If the ACTH stimulation test is abnormal (i.e., all cortisol values [prior to and after ACTH stimulation] are <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.

Also as specified in the flowchart (see Section 2), at certain time points, assessment of 17-hydroxyprogesterone, aldosterone, FSH, LH, progesterone, androstenedione, testosterone, DHEAS will be performed in conjunction with the basal cortisol assessment, and no ACTH stimulation test will be performed.

A sample for the determination of basal cortisol will be drawn in the morning of the time points specified in the flowchart (see Section 2), between 7h30 and 9h30. If at any of these time points basal cortisol value is <248 nmol/L (9 µg/dL), a retest will be done at the subsequent visit or at least within the next 8 weeks.

If basal cortisol is <248 nmol/L (9 µg/dL) at two consecutive scheduled visits, an ACTH stimulation test, as described above, will be done at the next scheduled visit or at least within the next 8 weeks with measurements of cortisol and 17-hydroxyprogesterone.

In case of clinical signs or symptoms or laboratory abnormalities (other than cortisol) indicative of adrenal insufficiency (see Section 6.5.5), the ACTH stimulation test should be done as soon as possible during an unscheduled visit.

In case of withdrawal due to pregnancy, no ACTH stimulation test needs to be performed, but basal assessments need to be performed.

For more details, please see the central laboratory manual.

6.4.9.2.3.2. Cohort 2: Children Aged ≥6 to <12 Years

At time points specified in the flowchart (see Section 2) an ACTH stimulation test will be performed for all subjects including measurements of cortisol and 17-hydroxyprogesterone. After a sample for the determination of these endocrine parameters has been drawn (T_0), 250 µg of tetracosactide or cosyntropin is injected intravenously over 2 minutes or intramuscularly and an additional blood sample is collected 60 minutes (T_{60}) after injection for the determination of cortisol and 17-hydroxyprogesterone.

Note: For subjects with laboratory findings suggestive of congenital adrenal hyperplasia at baseline, the Sponsor should be contacted for management guidance.

As specified in the flowchart (see Section 2), at certain time points, assessment of FSH, LH, androstenedione, testosterone, and DHEAS will be performed, in conjunction with basal cortisol and 17-hydroxyprogesterone.

As of Amendment 10, an ACTH stimulation test is no longer required at baseline and Week 24. Only in case basal cortisol is <248 nmol/L (9 µg/dL) at two consecutive visits, a reflex ACTH stimulation test, must be performed at the next scheduled visit or at least within the next 8 weeks, with measurements of cortisol and 17-hydroxyprogesterone.

If the ACTH stimulation test is abnormal (i.e., 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.

- If the repeat ACTH stimulation test results are normal, the subject should continue RPV treatment.
- If the repeat ACTH stimulation test results are abnormal, but the subject is asymptomatic the Sponsor will be notified.
- If the repeat ACTH stimulation test results are abnormal, and the subject has symptoms consistent with adrenal insufficiency (see Section 6.5.5) withdrawal of the subject should be discussed with the Sponsor.

In case of clinical signs or symptoms or laboratory abnormalities (other than cortisol) indicative of adrenal insufficiency (see Section 6.5.5), an ACTH stimulation test should be done as soon as possible during an unscheduled visit. If the ACTH stimulation test is abnormal (i.e., the cortisol value after ACTH stimulation is <500 nmol/L [18.1 µg/dL]), withdrawal of the subject should be discussed with the Sponsor.

In case of withdrawal due to pregnancy, no ACTH stimulation test needs to be performed, but basal assessments need to be performed.

For more details, please see the central laboratory manual.

6.4.9.2.4. Urinalysis

Urinalysis by dipstick for protein, RBC and glucose will be performed at specific time points (see flowchart, Section 2). If abnormal, a microscopic examination for WBC, RBC, and casts will be performed by the central laboratory.

Note: In the microscopic examination, observations other than the presence of WBC, RBC, and casts may also be reported by the laboratory.

At all time points throughout the trial (except at screening, Week 1, and Week 2), a urine pregnancy test will be performed for all girls of childbearing potential (see flowchart, Section 2). At baseline, a urine pregnancy test will be done prior to the first intake of RPV.

6.4.9.2.5. Hepatitis Serology/Viremia

A sample will be taken for hepatitis A, B, and C testing at baseline. Whenever clinically relevant, the investigator can request additional tests at other visits.

The hepatitis A infection status will be confirmed by the hepatitis A immunoglobulin M antibody. Hepatitis B infection status will be confirmed by hepatitis B surface antigen. The HCV infection status will be confirmed by HCV-antibody and if applicable also by qualitative

HCV RNA. Qualitative HCV RNA will only be performed, at baseline, in case the $CD4^+$ cell count at screening was <100 cells/mm^3 or in case the HCV-antibody test at screening was positive.

6.4.9.3. Cardiovascular Safety

At the time points specified in the flowchart (see Section 2), vital signs and ECG will be recorded. Any clinically relevant changes occurring from the signing of ICF onwards until the last trial-related visit must be recorded on the AE/HIV-Related Events section of the eCRF.

Please see Addendum 4: Cardiovascular Safety – Abnormalities for a detailed description of abnormalities.

6.4.9.3.1. Vital Signs

Systolic and diastolic blood pressure (SBP and DBP) must be measured standing and supine (after 5 minutes of rest). Standing and supine pulse must also be recorded at the same time points.

6.4.9.3.2. ECG

Central ECG readings will be performed by a central ECG lab. Instructions for ECG acquisition and ECG transmission will be described in the manual provided by the ECG lab. There will be 2 ECG reports: a preliminary report and a final report. The final report will be reviewed by a board certified cardiologist from the central ECG lab.

Both ECG reports generated by the central ECG lab will need to be interpreted for clinical significance, signed and dated by the investigator, and filed in the subject's medical record.

Whenever possible, the ECG should be taken around the expected C_{max} (i.e., 4 hours after intake of RPV).

6.4.9.4. Physical Examination

To evaluate the subject's eligibility, a full physical examination, in which all body parts need to be reviewed, will be performed at screening. In addition, a full physical examination will be performed at time points shown in the flowchart (see Section 2). This assessment 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, central nervous system, peripheral nervous system, musculoskeletal system, genitourinary system. It does not include rectal or vaginal examination unless clinically indicated. Any clinically relevant changes occurring from signing the ICF onwards must be recorded on the AE/HIV-related event sections of the eCRF.

At several time points (specified in the flowchart, Section 2) 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, and central nervous system. It does not include rectal or vaginal examination unless clinically indicated.

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

Body weight and height will be recorded at the visits specified in the flowchart (see Section 2). Growth will be followed regularly and evaluated consistently using standardized growth charts[30,31,32]. The subjects will be weighed in underwear, wearing no shoes. The same weighing scale will preferably be used at each visit. For the measurement of the height, the subjects will wear no shoes. The same stadiometer will preferably be used at each visit.

The assessment of pubertal development will be performed by a modified Tanner assessment[33] consisting of a discrete visual inspection and comparison to the illustrated Tanner scales (see Addendum 9: Tanner Scales). Tanner stages will be recorded at all visits indicated in the flowchart (see Section 2). For girls that have not yet had their first menses, the date of the first menses will be recorded as part of the evaluation of pubertal development at every visit. At screening, it will be assessed whether girls already have had their first menses.

Any clinically relevant changes in physical examination occurring from the signing of ICF onwards, until the last trial-related visit must be recorded on the AE /HIV-Related Event section of the eCRF.

6.4.10. Adherence Questionnaire

At all visits indicated in the flowchart (see Section 2) a number of Sponsor-selected questions from the Pediatric European Network for the Treatment of AIDS (PENTA) adherence questionnaire will be used to assess compliance. The adherence questionnaire will be self-administered by the subject at the visits as indicated at the flowchart. Depending on the age and literacy of the subject, the adherence questionnaire can be completed by the subject and/or by their parent or caregiver. If a subject and/or parent or caregiver has difficulties in completing the questionnaire, either because of the age, literacy or general health status, then the trial staff may assist in completing the questionnaire.

Once the subject and/or its parent or caregiver has completed the questionnaire, the site staff should review it for completeness. The questionnaire will be collected and the data will be entered into the trial database by the data manager.

If based on the review of the questionnaire, there seems to be a compliance issue, this should trigger additional compliance counseling by the investigator staff.

Note that the 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.

6.4.11. Evaluation for Depression

At all visits indicated in the flowchart (see Section 2) an evaluation will be done using questionnaires or other means, as in use at the site as part of local standard of care for this population, to assess whether the subject needs to be referred for a complete mental health assessment.

Subjects in whom a tendency for depression or suicidal thoughts is detected will be referred for a complete mental health assessment. Also, if the site staff feels that the child/adolescent has under-reported his/her symptoms, or if depression or suicidality are suspected, the subject should be referred for a complete mental health assessment.

6.4.12. Assessment of Palatability of RPV Formulation

Subjects who require RPV 15 mg (i.e. body weight <25 kg) or any other adjusted RPV dose should use a formulation other than the 25 mg tablet formulation (see Section 6.3.1). Understanding the taste preferences of children who take RPV as 2.5-mg tablets (which must be dispersed) is important as palatability of the study drug plays a pivotal role in achieving patient acceptance and therefore compliance to treatment. Taste acceptability will be assessed at Day 1 and Week 4 using a modified questionnaire form incorporating a 5 point hedonic facial scale (see Section 7.12, Addendum 12). This scale is a standard tool used in clinical trials to assess drug palatability in children[55,56].

6.5. Monitoring and Safety for Specific Toxicities

Guidelines in this section are applicable for the entire trial period, including the screening and follow-up period.

For grade 3 or 4 laboratory abnormalities, subjects 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 elevations in subjects with pre-existing diabetes
- Asymptomatic grade 3 or 4 glucose or triglyceride elevations, or asymptomatic grade 3 cholesterol elevations
- Asymptomatic grade 3 pancreatic amylase elevations in subjects with no history or concomitant disease of pancreatitis

AEs still ongoing at the end of the trial will be followed until satisfactory clinical resolution or stabilization. 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 one grade from baseline. Certain long-term AEs of ART cannot be followed to resolution within the setting of this trial; in these cases follow-up will be the responsibility of the investigator, which will be agreed upon with the Sponsor.

In case a treatment interruption (only allowed after the intensive PK visit) is needed during the treatment period in the event of a suspected toxicity, the subject will not automatically be withdrawn from the trial, as long as treatment interruption for the suspected toxicity does not exceed 4 weeks or the total cumulative duration of the treatment interruptions for suspected toxicities does not exceed 8 weeks (interruptions are counted cumulatively within a time frame of 48 weeks). In case a permanent discontinuation of study drug is needed, all ARV medication (i.e., RPV and background regimen) should be discontinued, considering the guidelines on-treatment discontinuation (Section 6.2.5) and specific considerations (Section 6.3.3).

Subjects who start ketoconazole treatment during the trial need to have an ACTH stimulation test performed 2 weeks into ketoconazole treatment (Cohort 1 only) and additional ECG monitoring is required (see Section 6.3.13.1).

Additional ECG monitoring is also required for subjects receiving CYP3A4 inhibitory comedications for >2 days, as well as for subjects receiving drugs associated with a risk of Torsade de Pointes for > 2 days (see Section 6.3.13.1). If the use of certain comedication warrants additional ECG monitoring, a pharmacokinetic sample should be taken within 10 minutes after this ECG on Days 3 to 7 after the start of the comedication in order to assess RPV concentration-safety relationships. The date and time of pharmacokinetic sampling and last intake of RPV should be recorded on the eCRF.

For subjects reporting cutaneous event/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:

6.5.1. Cutaneous Event/Rash

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

All the information regarding cutaneous reactions occurring after the first intake of study drug needs to be reported in the ‘Rash’ section of the eCRF within 24 hours and the trial site monitor needs to be informed. Cutaneous reactions occurring before the first intake of study drug are to be reported as medical events (see 1.4).

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),

ALP, bilirubin (total, direct and indirect), creatinine and a complete blood cell count (including hemoglobin, hematocrit, RBC count, WBC count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

If the etiology of the cutaneous event/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 eCRF.

When describing cases of cutaneous/rash reactions in the eCRF, the Rash Guidance Manual, part of the Investigator Manual, should be consulted.

Dermatologist fees for evaluating subjects who experience cutaneous reactions/rash will be reimbursed by the Sponsor.

Grade 1 Cutaneous Reaction/Rash:

A grade 1 rash is defined as localized macular rash.

Subjects may continue the ARV medication for a grade 1 rash.

The subject 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. If the rash is considered to be most likely due to concomitant illness or non-study drug, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Cetirizine (antihistamine), topical corticosteroids or antipruritic agents may be prescribed.

Referral to a dermatologist is optional for subjects experiencing a grade 1 rash.

Subjects should be informed that they should visit the clinic 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 Cutaneous Reaction/Rash:

A grade 2 cutaneous reaction/rash is defined as diffuse macular, maculopapular, or morbilliform rash or target lesions.

Subjects may continue the ARV medication for a grade 2 rash. The ARV medication may also be continued for any grade 2 rash with an increase in ALT/AST (<2x baseline) provided the subject is followed weekly with repeated testing. For subjects with a grade 2 rash and elevations of ALT/AST >2x baseline but <5x ULN, ARV medication should be interrupted and should only be restarted when the cutaneous reaction has resolved.

The subject should be advised to contact the investigator immediately if 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 for subjects experiencing a grade 2 rash.

Subjects should be informed that they should visit the clinic 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 Cutaneous Reaction/Rash:

A grade 3 cutaneous reaction/rash is defined as the following:

- Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae
- Cutaneous reaction/rash with superficial ulcerations of mucous membrane limited to one site
- Cutaneous reaction/rash with at least one of the following:
- Elevations of ALT/AST >2x baseline but at least 5x ULN*
- Fever ! 38°C or 100°F*
- Serum sickness-like reaction*
- Eosinophil count >1,000/mm^3*

* *added by the Sponsor.*

Subjects with a grade 3 rash will permanently discontinue the ARV medication and be withdrawn from the trial. 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 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.

Subjects should be informed that they should visit the clinic 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** (day of rash onset) of rash occurrence there are no increases in ALT/AST noted and there is no progression of rash (e.g., 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** of the rash occurrence the ALT/AST are at least 2 times baseline and at least 5 times ULN then safety blood samples should be taken daily for the first 5 days.

If on **Day 5** of rash the ALT/AST are at least 2 times baseline and at least 5 times ULN, 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 Cutaneous Reaction/Rash:

A grade 4 cutaneous reaction/rash is defined as 1 of the following:

- Extensive or generalized bullous lesions;
- Stevens-Johnson Syndrome (SJS);
- Ulceration of mucous membrane involving 2 or more distinct mucosal sites;
- Toxic Epidermal Necrolysis (TEN).

Subjects with a grade 4 rash will permanently discontinue the ARV medication and be withdrawn from the trial. 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.

Subjects should be informed that they should visit the clinic 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. Subjects should be hospitalized whenever medically appropriate for management of grade 4 rashes.

If on **Day 1** (day of rash onset) of rash occurrence there are no increases in ALT/AST noted and there is no progression of rash (e.g., 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** of the rash occurrence the ALT/AST levels are at least 2 times baseline and at least 5 times ULN then safety blood samples should be taken daily for the first 5 days.

If on **Day 5** of rash the ALT/AST levels are at least 2 times baseline and at least 5 times ULN, 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 2: Summary of Rash

Revised DAIDS Toxicity Grade	Definitions	Investigator Action	Rechallenge Instructions
Grade 1	Localized macular rash	May continue ARV medication.	NA
Grade 2	Diffuse macular, maculopapular rash or morbilliform rash or target lesions	May continue ARV medication.	NA
	Diffuse macular, maculopapular or morbilliform rash or target lesions with an increase in ALT/AST <2x baseline	May continue ARV medication.	NA
	Diffuse macular, maculopapular or morbilliform rash or target lesions with an increase in ALT/AST >2x baseline	Interrupt all ARV medication.	May resume all ART when rash has resolved
Grade 3	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae Cutaneous reaction/rash with superficial ulcerations of mucous membrane limited to one site Cutaneous reaction/rash with at least one of the following*: Elevations in ALT/AST (>2x baseline but at least 5x ULN); Fever (! 38 C or 100 F); Serum sickness-like reaction; Eosinophil >1,000/mm^3.	Discontinue ARV medication.	No
Grade 4	Extensive or generalized bullous lesions; Stevens-Johnson Syndrome (SJS); Ulceration of mucous membrane involving 2 or more distinct mucosal sites; Toxic Epidermal Necrolysis (TEN).	Discontinue ARV medication.	No

* Added by the Sponsor.

6.5.2. Acute Systemic Allergic Reaction

Management will be at the discretion of the investigator, taking into account the following protocol-defined procedures (also see Table 3), and should follow generally accepted medical standards.

Subjects planning to use ABC in their background regimen, who develop 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 (see Section 6.5.11.3).

Grade 1 (localized urticaria [wheals] with no medical intervention indicated):

Subjects may continue ARV medication for a grade 1 allergic reaction. The subject 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 or topical corticosteroids or antipruritic agents may be prescribed as long as these are in line with the package inserts of the N(t)RTIs in the background regimen or the (dis)allowed medication for RPV as indicated in Section 6.3.13.

Grade 2 (localized urticaria with medical intervention indicated or mild angioedema with no medical intervention indicated):

Subjects may continue ARV medication for a grade 2 allergic reaction. If there is any worsening of the allergic reaction, the subject should be advised to contact the investigator immediately and to discontinue ARV medication and be withdrawn from the trial.

Antihistamines or topical corticosteroids or antipruritic agents may be prescribed as long as these are in line with the package inserts of the N(t)RTIs in the background regimen or the (dis)allowed medication for RPV as indicated in Section 6.3.13.

Grade 3 (generalized urticaria, angioedema with medical intervention indicated or symptomatic mild bronchospasm) and **Grade 4** (acute anaphylaxis, life-threatening bronchospasm or laryngeal edema):

Subjects will permanently discontinue ARV medication and be withdrawn from the trial (see Section 6.2.5). Subjects will be treated as clinically appropriate. Standard management should be undertaken.

Table 3: Summary of Allergic Reaction

DAIDS Toxicity Grade	Definitions	Investigator Action Regarding ARV Medication (RPV and background regimen)
Grade 1	Localized urticaria [wheals] with no medical intervention indicated.	May continue ARV medication or have ARV medication interrupted at the investigator's discretion.
Grade 2	Localized urticaria with medical intervention indicated, or Mild Angiedema with no medical intervention indicated.	May continue ARV medication or have ARV medication interrupted at the investigator's discretion.
Grade 3	Generalized urticaria, or Angiedema with medical intervention indicated, or Symptomatic mild bronchospasm.	Permanently discontinue ARV medication (see Section 6.2.5).
Grade 4	Acute anaphylaxis, or Life-threatening bronchospasm, or Laryngeal edema.	Permanently discontinue ARV medication (see Section 6.2.5).

6.5.3. AST, ALT, and Total Bilirubin Elevation

Management will be at the discretion of the investigator, taking into account the following protocol-defined procedures (also see Table 4), and should follow generally accepted medical standards.

For grade 3 or 4 laboratory abnormalities, subjects 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.

Grade 1 AST or ALT Elevation (! 1.25 to &2.5x ULN) and Grade 2 AST or ALT Elevation (>2.5 to &5.0x ULN) with Grade 1 or 2 Total Bilirubin Elevation (! 1.1 to &2.5x ULN):

Subjects may continue ARV medication.

Grade 3 AST or ALT Elevation (>5.0 to &10.0x ULN) with Grade 1 or 2 Total Bilirubin Elevation (! 1.1 to &2.5x ULN):

Subjects are to interrupt all ARV medication, 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 (& grade 2), the subject may resume all ARV medication under the guidance of the investigator and preferably after the investigator has consulted with a Sponsor's Physician.

If a subject is required to interrupt all ARV medication due to a grade 3 AST or ALT elevation, and after restarting ARV medication he/she has a recurrence of grade 3 or grade 4 AST or ALT elevation, he/she will permanently discontinue the ARV medication and be withdrawn from the trial (see Section 6.2.5).

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

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

If a subject is diagnosed with acute viral hepatitis during the trial, the subject must be withdrawn from the trial immediately and the necessary follow-up visits performed (see Section 6.2.5). Subjects with chronic hepatitis B or C co-infection will be allowed to continue ARV treatment (RPV and background regimen) 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 subjects 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 he/she

will permanently discontinue the ARV medication and be withdrawn from the trial (see Section 6.2.5).

If for a subject co-infected with hepatitis B or C, experiencing grade 3 elevation in AST or ALT, ARV treatment is temporarily interrupted and he/she has a recurrence of grade 3 increase in AST or ALT after restarting ARV treatment, he/she may continue provided that ALP is not elevated to grade 2 or higher and total bilirubin is not elevated to grade 3 or higher, and he/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 all ARV treatment will be permanently discontinued and the subject will be withdrawn from the trial (see Section 6.2.5). If for the hepatitis B or C co-infected subject treatment is interrupted a second time because of a grade 3 elevation in AST or ALT, all ARV medication will be permanently discontinued and the subject will be withdrawn from the trial (see Section 6.2.5).

Grade 3 AST or ALT Elevation (>5.0 to &10.0x ULN) With at Least Grade 3 Total Bilirubin Elevation (>2.5x ULN) or Grade 4 AST or ALT Elevation (>10.0x ULN):

Subjects will permanently discontinue ARV medication and will be withdrawn from the trial (see Section 6.2.5).

Table 4: Summary of AST and ALT Elevations

DAIDS Toxicity Grade	Ranges	Investigator Action Regarding ARV Medication (RPV and background regimen)	Rechallenge instructions
Grade 1	≥1.25 to &2.5x ULN	May continue ARV medication if total bilirubin is & grade 2	NA
Grade 2	>2.5 to &5.0x ULN	May continue ARV medication if total bilirubin is & grade 2	NA
Grade 3	>5.0 to &10.0x ULN	**If total bilirubin is & grade 2:** Interrupt ARV medication until toxicity & grade 2; If co-infected with hepatitis B or C, ARV medication may be continued if ALP is & grade 2, bilirubin is & grade 3, and asymptomatic.	Allowed once If recurrence after restart of ARV medication, discontinue ARV medication permanently
		If total bilirubin is > grade 2: Discontinue ARV medication (see Section 6.2.5)	No
Grade 4	>10.0x ULN	Discontinue ARV medication (see Section 6.2.5)	No

NA: not applicable.

6.5.4. 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, subjects should be carefully evaluated and followed closely. An overview of the laboratory ranges to assign grading to a laboratory value for pancreatic amylase and lipase is provided in Addendum 2: DAIDS Table.

For confirmed asymptomatic grade 4 elevations of pancreatic amylase or confirmed asymptomatic grade 3 or grade 4 elevations of lipase, subjects should interrupt all ARV medication until pancreatic amylase returns to grade ≤3 or lipase returns to grade ≤2, at which time ARV medication could be re-introduced. If asymptomatic grade 4 elevations of pancreatic amylase or asymptomatic grade 3 or 4 lipase levels recur with reintroduction of ARV medication, all ARV medication should be permanently discontinued and the subject will be withdrawn from the trial (see Section 6.2.5).

6.5.5. 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 (see Section 2).

6.5.5.1. Cohort 1: Adolescents Aged ≥12 to <18 Years

In case of clinical signs or symptoms or laboratory abnormalities (other than cortisol) indicative for adrenal insufficiency, the ACTH stimulation test should be done as soon as possible during an unscheduled visit.

At the time point specific in the flowchart (see Section 2) an ACTH stimulation test will be performed for all subjects including measurements of cortisol, 17-hydroxyprogesterone, progesterone, DHEAS, androstenedione, testosterone, aldosterone, FSH, and LH (see Section 6.4.9.2.3). Cortisol, 17-hydroxyprogesterone, and aldosterone will be measured before, 30, and 60 minutes after ACTH stimulation; all other endocrine parameters will only be measured before ACTH stimulation. If the ACTH stimulation test is abnormal (i.e., all cortisol values [prior to and after ACTH stimulation] are <500 nmol/L [18.1µg/dL]), a retest needs to be performed at the next scheduled visit or at least within the next 8 weeks.

A sample for the determination of basal cortisol will be drawn in the morning of the time points specified in the flowchart (see Section 2), between 7h30 and 9h30. If at any of these time points basal cortisol value is <248 nmol/L (9 µg/dL), a retest will be done at the subsequent visit or at least within the next 8 weeks.

If basal cortisol is <248 nmol/L (9 µg/dL) at 2 consecutive scheduled visits, an ACTH stimulation test will be performed at the next scheduled visit or at least within the next 8 weeks with measurements of cortisol and 17-hydroxyprogesterone.

If the subject does not achieve a cortisol value of ≥500 nmol/L (18,1 µg/dL) on at least one of the 3 time points of cortisol measurement during the ACTH stimulation test (i.e., morning cortisol, 30 or 60 minutes after ACTH stimulation) at a trial visit where ACTH stimulation testing is done (as a result of 2 consecutive cortisol values being <248 nmol/L [9 µg/dL] or as a result of an

abnormal ACTH test at baseline or Week 48) and if this subject shows clinical signs and symptoms of adrenal insufficiency, which are evaluated in conjunction with other possible confounding factors (e.g., concomitant medication, AEs,…), withdrawal of the subject should be discussed with the Sponsor.

Appropriate clinical follow-up, including further endocrine evaluations, should be installed[24]. 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 trial. 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 treatment with RPV if this is in the best interest of the subject. 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 subjects may be hypovolemic, hyponatremic, or hyperkalemic. In such case initial therapy may consist of intravenously administered saline and dextrose. In a hypotensive patient, a 20 mL/kg bolus of isotonic sodium chloride solution given over the first hour may be necessary to restore their blood pressure. This bolus may be repeated if the blood pressure remains low. After results for the subject'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 child 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.

If the unscheduled ACTH test is performed further to the presence of signs and symptoms of adrenal insufficiency (as listed above), and the subject does not achieve a cortisol value ! 500 nmol/L (18.1 µg/dL) on at least one of the 3 time points of cortisol measurement during the ACTH stimulation test (i.e., morning cortisol, 30 or 60 minutes after ACTH stimulation), this should be discussed with the Sponsor, taking into account other possible confounding factors (e.g., concomitant medication, AEs,…), and the subject will be withdrawn from the trial if considered appropriate. Appropriate clinical follow-up, including further endocrine evaluations, should be installed[24].

As ketoconazole is known to have an intrinsic effect of inhibition of certain adrenal enzymes, resulting in decreased synthesis of certain adrenal hormones such as cortisol, subjects who start ketoconazole treatment during the trial need to have an ACTH stimulation test performed 2 weeks into ketoconazole treatment. If all cortisol values (prior to and after ACTH stimulation) are <500 nmol/L (18.1 µg/dL), and this subject has clinical signs and symptoms of adrenal insufficiency, which are evaluated in conjunction with other possible confounding factors (e.g.,

concomitant medication, AEs,…), the subject should be withdrawn from the trial after discussion with the Sponsor.

6.5.5.2. Cohort 2: Children Aged ≥6 to <12 Years

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, see Section 6.4.9.2.3.2.

If the unscheduled ACTH test is performed further to the presence of signs and symptoms of adrenal insufficiency (as listed above), and the subject does not achieve a cortisol value ! 500 nmol/L (18.1 µg/dL) on at least 1 of the time points of cortisol measurement during the ACTH stimulation test (i.e., morning cortisol or 60 minutes after ACTH stimulation), this should be discussed with the Sponsor, taking into account other possible confounding factors (e.g., concomitant medication, AEs,…), and the subject may discontinue RPV treatment and be withdrawn from the trial if considered appropriate.

Similar clinical follow-up as in Cohort 1, including seeking advice from an external endocrinologist if deemed appropriate will be applicable for Cohort 2.

6.5.6. Clinical Hepatitis

Non-Viral Hepatitis

Subjects 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.

Subjects with these signs and symptoms should seek medical attention immediately and hepatic parameters should be tested. All ARV medication must be permanently discontinued if the hepatitis is considered at least possibly related to RPV in the opinion of the investigator (see Section 6.2.5).

Viral Hepatitis

If acute viral hepatitis is diagnosed during the trial, the subject should be permanently withdrawn from the trial (see Section 6.2.5).

6.5.7. Neuropsychological Symptoms

Subjects should be informed that RPV may cause dizziness, insomnia, somnolence, impaired concentration and/or abnormal dreaming and instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

There have been reports of delusions and inappropriate behavior in subjects receiving licensed NNRTIs, especially in subjects 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 flowchart (see Section 2) an evaluation will be done using questionnaires or other means, as in use at the site as part of local standard of care for this population, to assess whether the subject needs to be referred for a complete mental health assessment. In case a tendency for depression or suicidal thoughts is detected, a mental health assessment will need to be performed. Subjects who experience symptoms of depression should contact the investigator immediately because discontinuation of the ARV medication (RPV and background regimen) may be required. Investigators should refer subjects reporting such symptoms for immediate psychiatric evaluation/medical intervention.

In case of grade 3 (alteration causing inability to perform usual social and functional activities) and grade 4 alterations in personality behavior or in mood (behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) or causing inability to perform basic self-care functions): the ARV medication must be permanently discontinued if the neuropsychological symptoms are considered at least possibly related to RPV in the opinion of the investigator (see Section 6.2.5).

6.5.8. Gastrointestinal Nausea (With or Without Vomiting)

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

Subjects planning to use ABC in their background regimen, who develop gastrointestinal nausea should be evaluated for the possibility of ABC hypersensitivity reaction and follow instructions related to clinically suspected hypersensitivity to ABC (see Section 6.5.11.3).

Grade 1 nausea (transient or intermittent; no or minimal interference with oral intake <24 hours) and **Grade 2 nausea** (persistent nausea resulting in decreased oral intake for 24-48 hours):

Subjects may continue with ARV medication and may be treated as needed with anti-emetics given orally or by suppository.

Grade 3 nausea (persistent nausea resulting in decreased intake for >48 hours or aggressive rehydration indicated):

Subjects developing grade 3 nausea will have all ARV medication interrupted. The subject will be treated as needed with anti-emetics given orally or by suppository. All ARV medication may be resumed when the nausea resolves to grade & 2.

If grade 3 nausea recurs after resuming the ARV medication despite the use of anti-emetics, subjects will discontinue all ARV medication and be withdrawn from the trial (see Section 6.2.5).

Grade 4 nausea (life-threatening consequences):

Subjects developing grade 4 nausea will permanently discontinue all ARV medication and will be withdrawn from the trial (see Section 6.2.5).

6.5.9. Diarrhea

Subjects planning to use ABC in their background regimen, who develop diarrhea should be evaluated for the possibility of ABC hypersensitivity reaction and follow instructions related to clinically suspected hypersensitivity to ABC (see Section 6.5.11.3).

Grade 1 diarrhea (transient or intermittent episodes of unformed stools or &3 stools over baseline per 24 hours) and **Grade 2 diarrhea** (persistent episodes of unformed to watery stools or &4-6 stools over baseline per 24 hours):

Subjects may continue ARV medication. Loperamide or diphenoxylate can be administered.

Grade 3 diarrhea (bloody diarrhea or ! 7 stools per 24 hours or intravenous fluid replacement required):

Subjects with grade 3 diarrhea will have all ARV treatment (RPV and background regimen) interrupted. All ARV medication (RPV and background regimen) may be resumed when the diarrhea resolves to grade &2.

If grade 3 diarrhea recurs after resuming the ARV medication despite the use of appropriate medication, subjects should permanently discontinue all ARV medication and will be withdrawn from the trial (see Section 6.2.5).

Grade 4 diarrhea (life-threatening consequences):

Subjects with grade 4 diarrhea will permanently discontinue all ARV medication and will be withdrawn from the trial (see Section 6.2.5).

6.5.10. Other Toxicities

Grade 1

Subjects who develop a grade 1 AE or laboratory toxicity may continue intake of the ARV medication.

Grade 2

Subjects who develop a grade 2 AE or laboratory toxicity may continue intake of the ARV medication based on the investigator's clinical judgment.

Grade 3

Subjects who develop a grade 3 AE or laboratory toxicity should temporarily interrupt all ARV medication and may resume all therapy when the AE or laboratory abnormality resolved to within one grade level of the subject's baseline but not higher than grade 2.

The following exceptions apply:

- Subjects with pre-existing diabetes who experience a glucose elevation of grade 3.
- Subjects who experience asymptomatic glucose, triglyceride or cholesterol elevations of grade 3.
- Subjects who experience asymptomatic pancreatic amylase elevations of grade 3 with no history or concomitant disease of pancreatitis.
- Subjects who experience an AE that is considered not related or doubtfully related to RPV.

Grade 4

Subjects experiencing a grade 4 AE or laboratory toxicity will permanently discontinue all ARV medication and will be withdrawn from the trial (see Section 6.2.5).

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

- Glucose elevation of grade 4 in subjects with pre-existing diabetes (see Section 6.5.11.1).
- Asymptomatic glucose or triglyceride elevations of grade 4 (see Sections 6.5.11.1 and 6.5.11.2).
- Confirmed pancreatic amylase and lipase elevations of grade 4 (see criterion 9) (see Section 6.5.4).
- A grade 4 AE (except cutaneous reaction/rash, allergic reaction, or neuropsychological event) that is considered not related or doubtfully related to RPV.

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

6.5.11. 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.

6.5.11.1. Hyperglycemia

Grade 3: 13.89-27.75 mmol/L (251-500 mg/dL);

Grade 4: >27.75 mmol/L (>500 mg/dL).

If elevated glucose levels are from a non-fasting blood draw, the draw should be repeated after a 10-hour fast. Management decisions should be based on fasted results. Subjects who experienced asymptomatic glucose elevations of grade 3 or 4 and subjects with pre-existing diabetes may continue ARV medication unless clinical assessment foresees an immediate health risk to the subject.

Subjects**, without pre-existing diabetes,** with persistent grade 3 or 4 glucose elevations despite appropriate antidiabetic medication/management should permanently discontinue ARV medication (see Section 6.2.5). Appropriate clinical management of hyperglycemia must be started in a timely fashion.

6.5.11.2. Hypertriglyceridemia and Hypercholesterolemia

Hypertriglyceridemia	**grade 3:** 8.49-13.56 mmol/L (751-1,200 mg/dL); **grade 4:** >13.56 mmol/L (>1,200 mg/dL).
Hypercholesterolemia	**grade 3:** >7.77 mmol/L (>300 mg/L); (**grade 4**: NA).

Management decisions should be based on fasted results. If elevated triglyceride or cholesterol levels are from a non-fasting blood draw, the draw should be repeated after a 10-hour fast. Subjects who experienced asymptomatic triglyceride elevations of grade 3 or 4 or cholesterol elevations of grade 3 may continue to receive ARV medication.

Hypertriglyceridemia and/or hypercholesterolemia should be treated according to the specific guidelines for treating HIV-infected subjects. 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 or clofibrate or niacin or a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, in addition to the usual counseling on diet and exercise. These medications should be introduced with caution. These medications may have overlapping adverse effects and niacin has the propensity to worsen the control of blood sugar in subjects with diabetes mellitus or a history of hyperglycemia.

6.5.11.3. Hypersensitivity Reactions

In clinical studies, approximately 5% of subjects receiving an ABC-containing product developed a hypersensitivity reaction, which in rare cases has been proven fatal[18].

At screening, all subjects without prior documented HLA-B*5701 negative results in whom the investigator considers ABC/3TC as the background regimen will be tested for HLA-B*5701. In those subjects where HLA-B*5701 is positive ABC/3TC cannot be administered[19]. In this case, the investigator should select AZT/3TC as the background regimen.

Also in case of switch to ABC due to intolerance of an N(t)RTI, the subject should test negative for HLA-B*5701.

It should also be noted that HLA screening and exclusion of HLA-B*5701 positive subjects does not completely eliminate the risk of hypersensitivity reactions.

Description of the Hypersensitivity Reaction

The ABC hypersensitivity reaction is characterized by the appearance of symptoms indicating multi-organ involvement. The majority of subjects have fever and/or rash as part of the syndrome; however reactions have occurred without rash or fever.

Symptoms can occur at any time during treatment with ABC, but usually appear within the first six weeks of initiation of treatment (median time to onset: 11 days). The symptoms worsen with continued therapy and can be life-threatening. These symptoms 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 or myolysis.

Physical findings may include rash (usually maculopapular or urticarial), lymphadenopathy or 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, or respiratory failure may occur.

Some subjects 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 of hypersensitivity has resulted in ABC being continued or re-introduced, leading to a more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for subjects presenting with symptoms of these diseases. If a hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (Ziagen®, Trizivir®, or Epzicom®/Kivexa®) should be restarted.

Management of Hypersensitivity Reactions

Subjects developing signs or symptoms of hypersensitivity MUST contact their doctor IMMEDIATELY for advice.

If a hypersensitivity reaction is diagnosed, the subject MUST discontinue ABC treatment IMMEDIATELY. The N(t)RTI background regimen will be replaced by alternative N(t)RTIs (Brand name versions or generics with tentative US FDA approval and/or WHO prequalified

drugs. If not available; generic drugs approved by the local Health Authorities or drugs procured by the UN international organizations can be allowed upon approval by the sponsor.). At all times the background regimen should consist of 2 N(t)RTIs and the subject's HIV-1 genotype at screening should show sensitivity to the alternative N(t)RTIs. The subject should be asked to return all unused supplies of the ABC-containing product for disposal to prevent an accidental rechallenge.

An ABC-containing medicinal product (Ziagen®, Trizivir®, or Epzicom®/Kivexa®) MUST NEVER be administered following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.

To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, the ABC-containing product should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis, or reactions to other medications).

Symptomatic support for ABC hypersensitivity may be indicated. This should include, for example, administration of intravenous fluids to subjects who develop hypotension. Antihistamines or corticosteroids have been used in cases of ABC hypersensitivity; however there are no clinical data demonstrating the benefit of these in the management of the reaction.

Laboratory and other investigations which may be useful in the evaluation and treatment of ABC hypersensitivity include, but may not be 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 Therapy

If therapy with ABC has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the subject did not have symptoms of a hypersensitivity reaction. If a hypersensitivity reaction cannot be ruled out, no medicinal product containing ABC (Ziagen®, Trizivir®, or Epzicom®/Kivexa®) should be restarted.

There have been infrequent reports of a hypersensitivity reaction following reintroduction of an ABC-containing product where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms, or a respiratory symptom). If a decision is made to restart any ABC-containing product in these subjects, this should be done only under direct medical supervision.

On very rare occasions hypersensitivity reactions have been reported in subjects who have restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to restart an ABC-containing product, this must be done only if the subject or others can access medical care readily.

Essential Subject Information

Subjects 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 subjects are fully informed regarding the following information on the hypersensitivity reaction:

- Subjects 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 subjects without prior documented HLA-B*5701 negative results in whom the investigator considers ABC/3TC as the background regimen will be tested for HLA-B*5701. In those subjects where HLA-B*5701 is positive ABC/3TC cannot be administered[19]. In addition, in case of switch to ABC during the trial, the subject should test negative for HLA-B*5701 (unless prior documented negative results are available).
- Subjects developing signs or symptoms possibly linked with a hypersensitivity reaction MUST CONTACT their doctor IMMEDIATELY.
- Subjects who are hypersensitive to ABC should be reminded that they must never take any ABC-containing medicinal product (Ziagen®, Trizivir®, or Epzicom®/Kivexa®) again.
- In order to avoid restarting the ABC-containing product, subjects who have experienced a hypersensitivity reaction should be asked to return the remaining tablets to the site.
- Subjects who have stopped taking an ABC-containing product for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.

Reporting of Hypersensitivity Reaction

All cases of potential ABC hypersensitivity should be reported as SAE (see 1.4).

6.5.11.4. Lactic Acidosis

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

A, sometimes fatal, syndrome of lactic acidosis, often associated with evidence of hepatic steatosis, is a recognized but rare complication of N(t)RTI therapy. This syndrome is felt to be secondary to mitochondrial toxicity induced by the inhibitory effect of N(t)RTIs on DNA polymerase gamma, a key enzyme needed for mitochondrial DNA synthesis. Current knowledge regarding this syndrome is incomplete. Obesity and prolonged N(t)RTI exposure may be risk factors. Symptoms of lactic acidosis frequently involve non-specific symptoms such as fatigue, weakness, and fever, but in the majority of cases also involve 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 over interpretation of lactic acid levels. N(t)RTI toxicity is only one 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 trial:

Symptomatic Hyperlactatemia

New, otherwise unexplained, and persistent (! 2 weeks) occurrence of one or more 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 >2x ULN should be repeated as soon as possible (local laboratory), generally within 1 week. If the second result confirms hyperlactatemia (>2x ULN), subjects should immediately interrupt their current ARV regimen (RPV and background regimen). Standard management should be initiated with follow-up to resolution. If causality is related to the background regimen only and NOT to the NNRTI regimen (RPV), N(t)RTIs must be changed. If causality is related to RPV, subjects must be withdrawn.

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

6.5.11.5. Renal Complications

Renal safety will be monitored by evaluating serum creatinine levels, eGFR, serum chemistry and urinalysis results at every trial visit.

If eGFR is decreased with >30% from baseline, the value must be confirmed by repeat testing within 72 hours using an unscheduled visit and ARV medication may be interrupted at the discretion of the investigator if the decrease in eGFR is confirmed. A sample for bioanalysis of RPV should be taken at the time of the unscheduled visit. If the abnormality is not confirmed, the subject may continue the ARV medication with continued close follow-up by the investigator. Unscheduled visits may be used to monitor renal function more closely. If the subject becomes 22 years of age or older during the study, the eGFR formula used for children cannot be used. In this case, the MDRD equation will be used.[58] The eGFR for these subjects calculated at 22 years of age or older cannot be compared with the original baseline, but with the value when first calculated with the MDRD equation. Long-term follow-up of subjects who develop nephrotoxicity should be discussed with the Sponsor. Subjects who change their background regimen or permanently discontinue ARV medication due to nephrotoxicity must attend scheduled, unscheduled or post-trial follow-up visits to characterize resolution of renal abnormalities. Follow-up visits (scheduled, unscheduled, or post-trial follow-up) will be conducted every 4 weeks and must be maintained until stabilization for 3 months with fluctuations of eGFR of less than 20% or return to baseline levels.

Note: In the Phase IIb trial with RPV there was a small decrease in mean creatinine clearance (Cl_{Cr}) from baseline, which appeared to reach a plateau at Week 4. There was an apparent dose relationship, with decreases in Cl_{Cr} being somewhat lower in the RPV 25 mg q.d. dose group than in the higher dose groups. The effect was more pronounced in subjects receiving TDF/FTC as the background regimen than in subjects receiving AZT/3TC. This small decrease was not considered to be clinically relevant. Also, in trial TMC278-TiDP6-C131 and the Phase III trial TMC278-TiDP6-C215, it was shown that RPV has no effect on the renal function, as assessed by the calculated cystatine C clearance[11,4].

6.5.11.6. Pancreatitis

Pancreatitis, which has been fatal in some cases, is a major clinical toxicity associated with didanosine (ddI) (with or without concomitant administration of TDF) and/or stavudine (d4T) therapy and has been reported with other ARVs. Pancreatitis must be considered whenever a subject receiving ddI (with or without concomitant administration of TDF) and/or d4T develops abdominal pain and nausea, vomiting, or elevated pancreatic amylase or lipase, and ddI (and/or TDF) and/or d4T use should be suspended until the diagnosis of pancreatitis is excluded.

In case the pancreatitis is considered at least possibly related to RPV, ARV medication must be permanently discontinued (see Section 6.2.5). The subject experiencing pancreatitis can however be rechallenged with the N(t)RTI background regimen, if pancreatitis is considered not related to TDF/FTC treatment.

6.5.11.7. Peripheral Neuropathy

Subjects 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.

6.6. Statistical Methods Planned and Determination of the Sample Size

The statistical analysis will be performed by a qualified vendor under the supervision/ responsibility of the Sponsor.

A general description of the statistical methods to be used to analyze the data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

An ITT population will be defined:

% The ITT population will be defined as the set of all subjects who have taken at least 1 dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

Cohort 1: Adolescents Aged ≥12 to <18 Years

A first analysis was performed when the first 11 Part 1a subjects had been treated for at least 2 weeks (or discontinued earlier). This was followed by an analysis when the Part 1b subjects had been treated for 4 weeks (+/-1 week) (or discontinued earlier). The objective of these analyses was to determine whether it is appropriate to continue with the 25 mg q.d. dose for the treatment of adolescents, based primarily on the pharmacokinetics of these Part 1 subjects and the short-term antiviral activity and safety. Short-term safety, tolerability, and efficacy were described in these analyses. All available data were included in these analyses, even if occurring after the time point for intensive pharmacokinetic sampling. The results of the Part 1 analysis indicated that no RPV dose adjustment was needed, as confirmed by the IDMC. In case the short-term Part 1 results would have indicated the need for a switch to a lower dose of RPV for all subjects up to a certain body weight, an additional analysis was to be done when all these subjects would have been treated for 4 weeks (+/-1week) with the weight-adjusted dose of RPV.

An analysis took place when all Part 1 subjects had reached 12 weeks of treatment (or discontinued earlier). This will be followed by an additional analysis when all Part 1 and Part 2 subjects have reached Week 12 of treatment (or discontinued earlier).

A primary analysis will take place when all subjects have reached Week 24 (or discontinued earlier). The objective of this Week 24 primary analysis is to evaluate the long-term safety,

tolerability and efficacy of RPV in HIV-1 infected adolescents. Another interim analysis will take place when all subjects have reached 48 weeks of treatment (or discontinued earlier). A final analysis (i.e., when all Cohort 1 subjects have reached 240 weeks of treatment [or discontinued earlier]) will take place when all Cohort 1 subjects have completed the trial.

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

A detailed SAP for each analysis will be written and signed off prior to database closure.

At the time of protocol amendment 6 writing, both the 24 week and 48 week analyses have been performed. For any changes to the planned analysis of Cohort 1, see the clinical study report of Cohort 1[53]. A summary of the 48-week results is provided in Section 6.1.2.2.

Cohort 2: Children Aged ≥6 to <12 Years

An initial analysis will be performed when the 5 Part 1 subjects of the mini-cohort have been treated for at least 4 weeks (or discontinued earlier). This will be followed by an overall analysis when all Part 1 subjects have been treated for at least 4 weeks (or discontinued earlier). The objective of these analyses is to determine whether it is appropriate to continue with the 25 mg q.d. dose for the treatment of children, based primarily on the pharmacokinetics of these subjects (samples taken after 14 to 18 days of RPV dosing) and the antiviral activity/efficacy and safety data. All available antiviral activity/efficacy and safety data will be included in these analyses, even if they have been obtained after the intensive pharmacokinetic sampling. If the results of these analyses indicate the need for an RPV dose adjustment for all or a part of the subjects in Part 1, an analysis (including the intensive pharmacokinetic evaluation after 14 to 18 days on the original and/or adjusted dose) will be performed after these subjects have been treated at least 4 weeks (or discontinued earlier) with the adjusted RPV dose. The overall Part 1 analysis and if applicable, analyses after RPV dose adjustments will be shared and discussed with the IDMC. For more details about the analyses, see Section 6.6.

Additional analyses will take place when all subjects in this C213 study have reached 12 and 24 weeks of treatment (or discontinued earlier). The objective of these analyses is to have the IDMC evaluate the interim safety, tolerability and efficacy results of RPV in children.

A final analysis will be performed when all Cohort 2 subjects have reached Week 48 (or discontinued earlier). The objective of this analysis is to evaluate the safety, tolerability and efficacy of RPV in HIV-1 infected children. The final, Week 48, analysis will be performed after a formal database lock.

A detailed statistical analysis plan (SAP) for each analysis will be written and signed off prior to database closure.

6.6.1. Determination of Sample Size

6.6.1.1. Cohort 1: Adolescents Aged ≥12 to <18 Years

Ten subjects in **Part 1a** was considered sufficient to allow for conclusions on the steady-state exposure after 2 weeks of treatment. After review of these Part 1a Week 2 data, it was decided to enroll the additional subjects in smaller cohorts and gather more intensive pharmacokinetic data in order to increase the precision of the pharmacokinetic parameter ratios. To ensure that all subjects have reached steady-state, intensive pharmacokinetic sampling in these additional subjects will be performed at Week 4 (+/-1 week).

If in Part 1, subjects had discontinued the trial before receiving their first dose of study drug, additional subjects could have been recruited to have 10 subjects starting treatment each in Part 1a and Part 1b. If subjects were prematurely withdrawn from the trial after starting treatment, for reasons other than drug tolerability/safety, additional subjects could have been recruited at the request of the Sponsor to aim for at least 10 evaluable subjects each at Week 2 (Part 1a)/Week 4 (Part 1b).

For **Part 2**, the precision of the efficacy parameter (proportion of subjects with viral load <50 HIV-1 RNA copies/mL, TLOVR) expressed as half the width of the (2-sided) 95% CI is presented in Table 5, assuming various sample sizes ranging from 25 to 35 subjects and response rates between 70 and 80%.

Table 5: Half the Width of the (2-Sided) 95% CI for Various Assumptions, Using a Normal Approximation

Sample size (N)	Response Rate (%)		
	70	75	80
25	18.0	17.0	15.7
30	16.4	15.5	14.3
35	15.2	14.4	13.3

Related to safety, Table 6 provides the probability of at least 1 occurrence of an AE for various sample sizes, provided the true incidence rate is 1%, 5%, and 10%.

Table 6: Probability (%) of ! 1 AE Reported, for Various Assumptions

Sample Size (N)	Incidence Rate (%)		
	10%	5%	1%
25	92.8	72.3	22.2
30	95.8	78.5	26.0
35	97.5	83.4	29.7

6.6.1.2. Cohort 2: Children Aged ≥6 to <12 Years

Approximately 40 subjects will be enrolled in this Cohort 2 (children aged ≥6 to <12 years) and in study TMC278HTX2002 (children aged ≥2 to <12 years with a body weight of ≥11 kg) combined: at least 12 subjects with a body weight of <25 kg, including 7 subjects with a body

weight of <20 kg. **As of Amendment 10** the PK data from this Cohort 2 will be combined with the data from pediatric study TMC278HTX2002.

Given that the body weights of the first 10 subjects enrolled in Cohort 2 were all towards the higher end, and data for subjects <25 kg were very limited (see addendum 7.11), it was decided to continue intensive PK evaluation for newly enrolled subjects with a body weight of <25 kg. At least 12 subjects in the body weight category <25 kg with intensive PK data across the 2 studies (Cohort 2 of this C213 study and study TMC278HTX2002) is considered sufficient to allow for conclusions on the steady-state exposure of RPV.

If in the mini-cohort, subjects discontinue the trial before receiving their first dose of study drug, additional subjects can be recruited to have 5 subjects starting treatment in the mini-cohort. If subjects discontinue the trial after starting treatment for reasons other than drug tolerability/safety, additional subjects can be recruited to have at least an additional 12 subjects with intensive pharmacokinetic data. Additional subjects may also be recruited if the Sponsor and IDMC deem it necessary to have additional subjects with intensive pharmacokinetic data because interpretation of the data is hampered by e.g., study drug adherence issues prior to the intensive pharmacokinetic sampling time point.

The precision of the efficacy parameter (proportion of subjects with viral load <50 HIV-1 RNA copies/mL, TLOVR) expressed as half the width of the (2-sided) 95% CI is presented in Table 7, assuming various sample sizes ranging from 10 to 25 subjects and response rates between 70 and 80%.

Table 7: Half the Width of the (2-Sided) 95% CI for Various Assumptions, Using the Clopper-Pearson Method

Sample size (N)	Response Rate (%)		
	70	**75**	**80**
10	29.3	28.1	26.5
15	24.3	23.2	21.9
20	21.2	20.2	19.0
25	19.0	18.1	16.9

Related to safety, Table 8 provides the probability of at least 1 occurrence of an AE for various sample sizes, provided the true incidence rate is 1%, 5%, and 10%.

Table 8: Probability (%) of ≥1 AE Reported, for Various Assumptions

Sample Size (N)	Incidence Rate (%)		
	10%	**5%**	**1%**
10	65.1	40.1	9.6
15	79.4	53.7	14.0
20	87.8	64.2	18.2
25	92.8	72.3	22.2

6.6.2. Statistical Analyses

6.6.2.1. Initial Subject and Disease Characteristics

All demographic (age, height, weight, gender, body mass index [BMI], ethnic origin) and other initial subject characteristics (smoking habits, physical examination, medical and surgical history, concomitant diseases) will be tabulated and analyzed descriptively.

6.6.2.2. Efficacy

6.6.2.2.1. Plasma viral load

Throughout the analysis, plasma viral load will be $\log_{10}$ transformed. Plasma viral load reported as <50 HIV-1 RNA copies/mL will be scored as 49 HIV-1 RNA copies/mL, if not otherwise mentioned.

Parameters:

- The change in plasma viral load from baseline at Week 2 /Week 4 (IDMC analyses only).
- Proportion of subjects with a viral load <50 and <400 HIV-1 RNA copies/mL at all time points, and time to achieve these;
- Proportion of subjects with a decrease from baseline in plasma viral load of 1.0 $\log_{10}$ at Week 12
- Change from baseline in $\log_{10}$ viral load;

6.6.2.2.1.1. Analysis

An outcome analysis using "Snapshot" approach will be performed, i.e., viral load <50 and <400 HIV-1 RNA copies/mL observed and missing = failure (M=F). The Snapshot analysis is based on the last observed viral load data within the visit window (i.e. Weeks 24 and 48). Subjects who switched N(t)RTIs for tolerability reasons not allowed per protocol (see Section 6.3.5) will be considered as failures for this Snapshot approach. Proportion responders will be expressed as percentages with Clopper-Pearson 95% CI at each time point.

Raw data and changes in $\log_{10}$ plasma viral load will be descriptively and graphically presented.

Changes in plasma viral load will be part of the efficacy analysis and will not be reported as AEs/SAEs.

6.6.2.2.2. Immunology

Immunology parameter:

- The change from baseline in CD4+ cell count (absolute and %).

The analysis will be based on observed values and on imputed values using NC = F, i.e., subjects who prematurely discontinued the trial and will have their $CD4^+$ cell count following discontinuation imputed with the baseline value (resulting in a change of 0), and will have LOCF for intermediate missing values.

Raw data and changes versus baseline will be descriptively and graphically presented.

6.6.2.3. Resistance Determinations

The results of the viral pheno- and genotypes will be evaluated by the Protocol Virologist.

Relevant changes in the viral phenotype and genotype and archived resistance, as applicable, will be tabulated and described, particularly for subjects with virologic failure. Changes in viral phenotype and genotype will not be regarded as AEs.

Furthermore, phenotypic resistance data, including the fold change in EC_{50} values, of RPV and other ARVs will be described.

6.6.2.4. Pharmacokinetic Parameter Analyses

Applicable for Intensive PK data:

Pharmacokinetic and statistical analyses of the results will be done using WinNonlin Professional™ (Pharsight Corporation, Mountain View, California, U.S.A.), Microsoft Excel® (Microsoft Redmond, Washington, U.S.A.) and/or SAS (SAS Institute Inc. Cary, NC, U.S.A.). A non-compartmental model with extravascular input will be used for the pharmacokinetic analysis.

Based on the individual plasma concentration-time data, using the actual sampling times (see the flowchart for scheduled sampling times, Section 2), the following pharmacokinetic parameters are to be derived for RPV:

At the Week 2 or Week 4 visit for Cohort 1, and at the Week 2 visit (Day 14-18) for Cohort 2: C_{0h}, C_{min}, t_{max}, C_{max}, AUC_{24h}, $C_{ss,av}$, CL/F, fluctuation index

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

- C_{0h}: predose plasma concentration;
- C_{min}: minimum plasma concentration between 0 hour and τ (τ = dosing interval);
- C_{max}: maximum plasma concentration;
- t_{max}: time to reach the maximum plasma concentration;
- AUC_{24h}: AUC from time of administration up to 24 hours post dosing, calculated by linear trapezoidal summation;

- $C_{ss,av}$: average steady-state plasma concentration, calculated by AUCτ / τ at steady-state (τ = dosing interval);
- CL/F: total apparent plasma clearance at steady-state, calculated by dose/AUC_{24h}.
- Fluctuation index, i.e., percentage fluctuation (variation between maximum and minimum plasma concentration at steady-state), calculated as 100x ([C_{max} - C_{min}] / $C_{ss,av}$).

The mean AUC_{24h} in adolescents and children will be compared separately with the mean AUC_{24h} of the 25 mg q.d. dose in adults.

Descriptive statistics will be calculated for the plasma concentrations of RPV at each time point and for the derived pharmacokinetic parameters. Statistics will include sample size (n), mean, standard deviation (SD), percentage of coefficient of variation (%CV), geometric mean, median, minimum, and maximum.

For each subject, 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.

Applicable for population PK analysis:

Based on the individual plasma concentration-time data, using the actual medication intake and sampling times, pharmacokinetic parameters of RPV will be derived for all subjects, using population pharmacokinetic modeling. The intensive pharmacokinetic sampling data will also be included in the population pharmacokinetic model for further evaluation of the RPV dose with modeling and simulation. CCI [redacted] CCI [redacted]

The mean AUC_{24h} in adolescents and children will be compared separately with the mean AUC_{24h} of the 25 mg q.d. dose in adults.

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

Efficacy and safety parameters will be subjected to a pharmacokinetic/pharmacodynamic analysis. Various efficacy and safety parameters will be linked to the pharmacokinetics of RPV applying graphical tools and statistical models, if applicable.

6.6.2.5. Safety

6.6.2.5.1. Adverse Events/HIV-Related Events

Type (system organ class, preferred term) and incidence of all AEs and HIV-related events, between the signing of ICF and last trial-related activity, will be tabulated per trial period (i.e., screening, the treatment period and follow-up). Separate tabulations will be made by severity, drug relationship, and outcome of the AEs. Separate tabulations and listings will be made for those subjects who have discontinued the trial for an AE/HIV-related event, or who experienced a grade 3 or 4 AE, or an SAE.

6.6.2.5.2. Clinical Laboratory Tests

For the clinical laboratory data, descriptive statistics will be generated for all tests performed (actual values and changes from baseline). Statistics to be presented include number of observations (n), mean, standard deviation, median, minimum and maximum.

Additionally, for the tests available, laboratory abnormalities will be calculated according to the DAIDS grading table (see Addendum 2: DAIDS Table). Worst toxicity grade after baseline will be cross-tabulated versus baseline. Separate tabulations and listings will be provided for those subjects who develop a grade 3 or 4 laboratory toxicity. For tests for which no DAIDS grading exists, a cross-tabulation versus baseline (with classes below/within/above normal range) will be performed.

Clinically significant changes in laboratory values, other diagnostic tests (except for changes in resistance pattern, plasma viral load, and $CD4^+$ cell counts), and intercurrent illnesses are AEs.

Descriptive statistics of the actual values and changes from baseline of the endocrine assessments at 30 minutes (Cohort 1 only) and 60 minutes after ACTH stimulation as well as for the maximal increment after ACTH stimulation will be presented for the respective analytes (cortisol, 17-hydroxyprogesterone, aldosterone [Cohort 1 only]). In addition, the proportion of subjects with values at all 3 (Cohort 1) and all available (Cohort 2) assessments during ACTH stimulation (before, 30 minutes [Cohort 1 only] and 60 minutes after ACTH stimulation) of cortisol being <500 nmol/L (18.1 µg/dL), will be tabulated.

Results of the ACTH stimulation test during the concomitant use of ketoconazole (Cohort 1 only) will be described separately.

Descriptive statistics of the actual values and changes from baseline of the other endocrine assessments will be generated.

6.6.2.5.3. Cardiovascular Safety

The effects on cardiovascular and vital signs parameters will be evaluated by means of descriptive statistics (actual values and changes from baseline) and frequency tabulations.

Statistics to be presented include number of observations (n), mean, standard deviation, median, minimum and maximum.

Vital signs include pulse, SBP and DBP. For the BP parameters, the toxicity definition of the DAIDS grading (see Addendum 2: DAIDS Table) will be applied. The percentage of subjects with abnormal values (see Section 7.4 for age specific details) will be tabulated at each specific time point.

The ECG parameters that will be analyzed are heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB (QT corrected for heart rate according to Bazett[34]) and QTcF (QT corrected for heart rate according to Fridericia[35]). For the ECG parameters, the toxicity definition of the DAIDS grading (see Addendum 2: DAIDS Table) will be applied. The percentage of subjects with increases in QTc of <30, 30-60, or >60 milliseconds from screening and abnormal QTc, PR, QRS interval, RR interval values (see Section 7.4 for age specific details) will be tabulated at each time point.

All important abnormalities from the ECG readings will be reported.

6.6.2.5.4. Physical Examination

Physical examination findings will be tabulated at each time point.

Body weight and height will be analyzed descriptively (actual values and changes from baseline). Statistics to be presented include number of observations (n), mean, standard deviation, median, minimum and maximum. These tables will include shifts from baseline values to allow detection of relevant changes in individuals.

6.6.2.6. Diaries

A subject listing will be created with the date and time of intake of RPV from the start of treatment with RPV 25 mg q.d. (or adjusted dose if applicable) until the day of intensive pharmacokinetic sampling.

6.6.2.7. Questionnaires

Subject listings will be created so that adherence can be checked on an individual basis. The answers to the different questions will be tabulated at each time point

6.7. Data Quality Assurance

See Data Quality Assurance (Part II, Section 8).

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Addenda

7.1. Addendum 1: Trial Contact Persons

An up-to-date version of the contact details of Sponsor, central laboratories and other third parties will be available in the investigator site file.

7.2. Addendum 2: DAIDS Table

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS. PUBLISH DATE: DECEMBER, 2004

Quick Reference

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS grading table") is a descriptive terminology to be utilized for AE reporting in this trial. A grading (severity) scale is provided for each AE term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical AE that is not identified in the DAIDS grading table, use the category "Estimating Severity Grade" located at the top of the table on the following page.

Grading Adult and Pediatric AEs

The DAIDS grading table includes parameters for grading both adult and pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both adult and pediatric populations, separate sets of parameters for adult and/or pediatric populations (with specified respective age ranges) are provided. If there is no distinction in the table between adult and pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both adult and pediatric events of that type.

Determining Severity Grade

If the severity of an AE could fall under either one of 2 grades (e.g., the severity of an AE could be either grade 2 or grade 3), select the higher of the 2 grades for the AE.

Note: The laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

Basic self-care functions	Adult: activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young children: activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
Usual social & functional activities	Adult: adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children: activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).
Medical intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
Operative intervention	Surgical OR other invasive mechanical procedures.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical AE NOT identified elsewhere in this DAIDS grading table	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 Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic 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
Fatigue Malaise	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 fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C–38.6°C	38.7°C–39.3°C	39.4°C–40.5°C	>40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection site reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	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 (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5% – 9% loss in body weight from baseline	10% – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult >15 years	Erythema OR Induration of 5x 5 cm – 9x 9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema >9 cm any diameter (or >81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤2.5 cm diameter	Erythema OR Induration OR Edema >2.5 cm diameter but <50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with <48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by trial participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction/rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Cutaneous reaction /rash with superficial ulcerations of mucous membrane limited to 1 site[f] OR Cutaneous reaction/rash with at least 1 of the following[f]: elevation of AST and/or ALT >2x baseline but at least >5x ULN[f]; fever (>38°C or 100°F)[f]; eosinophils >1,000/mm^3[f]; serum sickness-like reaction[f]	Extensive or generalized bullous lesions OR SJS OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR TEN
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection site reactions: Pruritis associated with injection)	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
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Nonurgent medical intervention indicated	Symptomatic, non-life-threatening AND Nonurgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

[f] Revised by the Sponsor.

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Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac ischemia/ infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial Infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤2 units packed RBCs (for children ≤10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension[a]				
Adult >17 years (with repeat testing at same visit)	>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 (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric ≤17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, i.v. fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult >16 years	PR interval 0.21–0.25 s	PR interval >0.25 s	Type II 2nd degree AV block OR Ventricular pause >3.0 s	Complete AV block
Pediatric ≤16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

[a] Revised by the Sponsor.

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged QTc					
	Adult >16 years	Asymptomatic, QTc interval 0.45–0.47 s OR Increase in interval <0.03 s above baseline	Asymptomatic, QTc interval 0.48–0.49 s OR Increase in interval 0.03–0.05 s above baseline	Asymptomatic, QTc interval ≥0.50 s OR Increase in interval ≥0.06 s above baseline	Life-threatening consequences, e.g., Torsade de Pointes or other associated serious ventricular dysrhythmia
	Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450–0.464 s	Asymptomatic, QTc interval 0.465–0.479 s	Asymptomatic, QTc interval ≥0.480 s	Life-threatening consequences, e.g., Torsade de Pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism		NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)		Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)		NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL					
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 (e.g., tube feeding or TPN)
Ascites		Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥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 4–6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥7 stools per 24-hour period OR i.v. fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric <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	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia - Odynophagia and Proctitis	Erythema of the Mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Aggressive rehydration indicated (e.g., i.v. fluids)	Life-threatening consequences (e.g., hypotensive shock)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND 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 (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., i.v. fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	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	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	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
CNS ischemia (acute)	NA	NA	Transient ischemic Attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay Pediatric ≤ 16 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 (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	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

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	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
Seizure: (new onset) **Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (nonrepetitive) without change in seizure character OR Infrequent breakthrough seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure **Pediatric <18 years**	Seizure, generalized onset with or without secondary generalization, lasting <5 minutes with <24 hours postictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with <24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
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

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
RESPIRATORY					
Bronchospasm (acute)		FEV1 or peak flow reduced to 70%–80%	FEV1 or peak flow 50%–69%	FEV1 or peak flow 25%–49%	Cyanosis OR FEV1 or peak flow <25% OR Intubation
Dyspnea or respiratory distress					
	Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
	Pediatric <14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90%–95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL					
Arthralgia See also Arthritis		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 See also Arthralgia		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
Bone Mineral Loss					
	Adult ≥21 years	BMD t-score -2.5 to -1.0	BMD t-score <-2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
	Pediatric <21 years	BMD z-score -2.5 to -1.0	BMD z-score <-2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Myalgia (noninjection site)	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	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical trial agents) For other cervicitis see Infection: Infection (any other than HIV infection)	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
Cervicitis (clinical exam) (For use in studies evaluating topical trial agents) For other cervicitis, see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption <25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25%–49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50%–75% total surface	Epithelial disruption >75% total surface
Intermenstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	IMB not greater in duration or amount than usual menstrual cycle	IMB greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	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

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Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical trial agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	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
Vulvovaginitis (clinical exam) (Use in studies evaluating topical trial agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25%–49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50% – 75% total surface	Vaginal perforation OR Epithelial disruption >75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (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)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by trial participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

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Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar nonketotic coma)
Gynecomastia	Detectable by trial participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic 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 (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic 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 (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by trial participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

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Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY *Standard International Units are listed in italics*				
Absolute $CD4^+$ count **Adult and Pediatric >13 years** (HIV negative only)	300–400/mm³ *300–400/µL*	200–299/mm³ *200–299/µL*	100–199/mm³ *100–199/µL*	<100/mm³ *<100/µL*
Absolute lymphocyte count **Adult and Pediatric >13 years** (HIV negative only)	600–650/mm³ *0.600x 10^9 – 0.650x 10^9/L*	500–599/mm³ *0.500x 10^9 – 0.599x 10^9/L*	350–499/mm³ *0.350x 10^9 – 0.499x 10^9/L*	<350/mm³ *<0.350x 10^9/L*
Absolute neutrophil count				
Adult and Pediatric >7 days	1,000–1,300/mm³ *1.000x 10^9 – 1.300x 10^9/L*	750–999/mm³ *0.750x 10^9 – 0.999x 10^9 /L*	500–749/mm³ *0.500x 10^9 – 0.749x 10^9/L*	<500/mm³ *<0.500x 10^9/L*
Infant[a,b] 2 – ≤7 days	1,250–1,500/mm³ *1.250x 10^9 – 1.500x 10^9/L*	1,000–1,249/mm³ *1.000x 10^9 – 1.249x 10^9/L*	750–999/mm³ *0.750x 10^9 – 0.999x 10^9/L*	<750/mm³ *<0.750x 10^9/L*
Infant[a,b] 1 day	4,000–5,000/mm³ *4.000x 10^9 – 5.000x 10^9/L*	3,000–3,999/mm³ *3.000x 10^9 – 3.999x10^9/L*	1,500–2,999/mm³ *1.500x 10^9 – 2.999x 10^9/L*	<1,500/mm³ *<1.500x 10^9/L*
Fibrinogen, decreased[c]	100–200 mg/dL *1.00–2.00 g/L* OR ≥0.75 to <1.00x lower limit of laboratory normal range (LLN)	75–99 mg/dL *0.75–0.99 g/L* OR ≥0.50 to <0.75x LLN	50–74 mg/dL *0.50–0.74 g/L* OR ≥0.25 to <0.50x LLN	<50 mg/dL *<0.50 g/L* OR <0.25x LLN OR Associated with gross bleeding
Hemoglobin[d]				
Adult and Pediatric ≥57 days (HIV positive only)	8.5–10.0 g/dL *5.2–6.1 mmol/L*	7.5–8.4 g/dL *4.6–5.1 mmol/L*	6.5–7.4 g/dL *3.9–4.5 mmol/L*	<6.5 g/dL *<3.9 mmol/L*
Adult and Pediatric ≥57 days (HIV negative only)	10.0–10.9 g/dL *6.1–6.6 mmol/L* OR Any decrease 2.5–3.4 g/dL *1.5–2.0 mmol/L*	9.0–9.9 g/dL *5.5–6.0 mmol/L* OR Any decrease 3.5–4.4 g/dL *2.1–2.6 mmol/L*	7.0–8.9 g/dL *4.2–5.4 mmol/L* OR Any decrease ≥4.5 g/dL *≥2.7 mmol/L*	<7.0 g/dL *<4.2 mmol/L*
Infant[a,b] 36–56 days (HIV positive or negative)	8.5–9.4 g/dL *5.2–5.7 mmol/L*	7.0–8.4 g/dL *4.2–5.1 mmol/L*	6.0–6.9 g/dL *3.6–4.1 mmol/L*	<6.0 g/dL *<3.6 mmol/L*

[a] Values are for term infants.
[b] Use age and sex-appropriate values (e.g., bilirubin), including preterm infants.
[c] Revised by the Sponsor.
[d] Revised by the Sponsor; monomer conversion factor used for conversion from g/dL to mmol/L

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant[a,b] 22 – 35 days (HIV positive or negative)	9.5–10.5 g/dL *5.8–6.4 mmol/L*	8.0–9.4 g/dL *4.8–5.7 mmol/L*	7.0–7.9 g/dL *4.2–4.7 mmol/L*	<7.00 g/dL *<4.2 mmol/L*
Infant[a,b] 1 – 21 days (HIV positive or negative)	12.0–13.0 g/dL *7.3–7.9 mmol/L*	10.0–11.9 g/dL *6.1–7.2 mmol/L*	9.0–9.9 g/dL *5.5–6.0 mmol/L*	<9.0 g/dL *<5.5 mmol/L*
International normalized ratio (INR) of prothrombin time (PT)[c]	≥1.1 to ≤1.5x ULN	>1.5 to ≤2.0x ULN	>2.0 to ≤3.0x ULN	>3.0x ULN
Methemoglobin	5.0%–10.0%	10.1%–15.0%	15.1%–20.0%	>20.0%
PT[c,d]	≥1.1 to ≤1.25x ULN	>1.25 to ≤1.50x ULN	>1.50 to ≤3.00x ULN	>3.00x ULN
Partial thromboplastin Time[c]	≥1.1 to ≤1.66x ULN	>1.66 to ≤2.33x ULN	>2.33 to ≤3.00x ULN	>3.00x ULN
Platelets, decreased	100,000–124,999/mm³ *100.000x 10^9–124.999x 10^9/L*	50,000–99,999/mm³ *50.000x 10^9–99.999x 10^9/L*	25,000–49,999/mm³ *25.000x 10^9–49.999x 10^9/L*	<25,000/mm³ *<25.000x 10^9/L*
WBC, decreased	2,000–2,500/mm³ *2.000x 10^9–2.500x 10^9/L*	1,500–1,999/mm³ *1.500x 10^9–1.999x 10^9/L*	1,000–1,499/mm³ *1.000x 10^9–1.499x 10^9/L*	<1,000/mm³ *<1.000x 10^9/L*
CHEMISTRIES ***Standard International Units are listed in italics***				
Acidosis	NA	pH < normal, but ≥7.3	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0–2.9 g/dL *20–29 g/L*	<2.0 g/dL *<20 g/L*	NA
ALP[c]	≥1.25 to ≤2.5x ULN[b]	>2.5 to ≤5.0x ULN[b]	>5.0 to ≤10.0x ULN[b]	>10.0x ULN[b]
Alkalosis	NA	pH > normal, but ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT (SGPT)[c]	≥1.25 to ≤2.5x ULN	>2.5 to ≤5.0x ULN	>5.0 to ≤10.0x ULN	>10.0x ULN
AST (SGOT)[c]	≥1.25 to ≤2.5x ULN	>2.5 to ≤5.0x ULN	>5.0 to ≤10.0x ULN	>10.0x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0–15.9 mEq/L *11.0–15.9 mmol/L*	8.0–10.9 mEq/L *8.0–10.9 mmol/L*	<8.0 mEq/L *<8.0 mmol/L*

[a] Values are for term infants.
[b] Use age- and sex-appropriate values (e.g., bilirubin), including preterm infants.
[c] Revised by the Sponsor.
[d] If the local laboratory is reporting PT as percentage, only INR value will be considered for reporting PT related abnormalities and AEs.

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Bilirubin (Total)[a]				
Adult and Pediatric >14 days	≥1.1 to ≤1.5x ULN	>1.5 to ≤2.5x ULN	>2.5 to ≤5.0x ULN	>5.0x ULN
Infant[b,c] ≤14 days (non-hemolytic)	NA	20.0–25.0 mg/dL *342–428 µmol/L*	25.1–30.0 mg/dL *429–513 µmol/L*	>30.0 mg/dL *>513.0 µmol/L*
Infant[b,c] ≤14 days (hemolytic)	NA	NA	20.0–25.0 mg/dL *342–428 µmol/L*	>25.0 mg/dL *>428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥7 days	10.6–11.5 mg/dL *2.65–2.88 mmol/L*	11.6–12.5 mg/dL *2.89–3.13 mmol/L*	12.6–13.5 mg/dL *3.14–3.38 mmol/L*	>13.5 mg/dL *>3.38 mmol/L*
Infant[b,c] <7 days	11.5–12.4 mg/dL *2.88–3.10 mmol/L*	12.5–12.9 mg/dL *3.11–3.23 mmol/L*	13.0–13.5 mg/dL *3.24–3.38 mmol/L*	>13.5 mg/dL *3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥7 days	7.8–8.4 mg/dL *1.95–2.10 mmol/L*	7.0–7.7 mg/dL *1.75–1.94 mmol/L*	6.1–6.9 mg/dL *1.53–1.74 mmol/L*	<6.1 mg/dL *<1.53 mmol/L*
Infant[b,c] <7 days	6.5–7.5 mg/dL *1.63–1.88 mmol/L*	6.0–6.4 mg/dL *1.50–1.62 mmol/L*	5.50–5.90 mg/dL *1.38–1.49 mmol/L*	<5.50 mg/dL *<1.38 mmol/L*
Cardiac troponin I	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T	NA	NA	NA	≥0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥18 years	200–239 mg/dL *5.18–6.19 mmol/L*	240–300 mg/dL *6.20–7.77 mmol/L*	>300 mg/dL *>7.77 mmol/L*	NA
Pediatric <18 years	170–199 mg/dL *4.40–5.15 mmol/L*	200–300 mg/dL *5.16–7.77 mmol/L*	>300 mg/dL *>7.77 mmol/L*	NA
Creatine kinase[a]	≥3.0 to ≤5.9x ULN[c]	>5.9 to ≤9.9x ULN[c]	>9.9 to ≤19.9x ULN[c]	>19.9x ULN[c]
Creatinine[a]	≥1.1 to ≤1.3x ULN[c]	>1.3 to ≤1.8x ULN[c]	>1.8 to ≤3.4x ULN[c]	>3.4x ULN[c]
Glucose, serum, high				
Non-fasting	116–160 mg/dL *6.44–8.88 mmol/L*	161–250 mg/dL *8.89–13.88 mmol/L*	251–500 mg/dL *13.89–27.75 mmol/L*	>500 mg/dL *>27.75 mmol/L*
Fasting	110–125 mg/dL *6.11–6.94 mmol/L*	126–250 mg/dL *6.95–13.88 mmol/L*	251–500 mg/dL *13.89–27.75 mmol/L*	>500 mg/dL *>27.75 mmol/L*

[a] Revised by the Sponsor.
[b] Values are for term infants.
[c] Use age- and sex-appropriate values (e.g., bilirubin), including preterm infants.

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, low				
Adult and Pediatric ≥1 month	55–64 mg/dL *3.05–3.55 mmol/L*	40–54 mg/dL *2.22–3.00 mmol/L*	30–39 mg/dL *1.67–2.21 mmol/L*	<30 mg/dL *<1.67 mmol/L*
Infant[a,b] <1 month	50–54 mg/dL *2.78–3.00 mmol/L*	40–49 mg/dL *2.22–2.77 mmol/L*	30–39 mg/dL *1.67–2.21 mmol/L*	<30 mg/dL *<1.67 mmol/L*
Lactate	<2.0x ULN without acidosis	≥2.0x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥18 years	130–159 mg/dL *3.37–4.12 mmol/L*	160–190 mg/dL *4.13–4.90 mmol/L*	≥191 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric >2 – <18 Years	110–129 mg/dL *2.85–3.34 mmol/L*	130–189 mg/dL *3.35–4.90 mmol/L*	≥190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase[c]	≥1.1 to ≤1.5x ULN	>1.5 to ≤3.0x ULN	>3.0 to ≤5.0x ULN	>5.0x ULN
Magnesium, serum, low	1.2–1.4 mEq/L *0.60–0.70 mmol/L*	0.9–1.1 mEq/L *0.45–0.59 mmol/L*	0.6–0.8 mEq/L *0.30–0.44 mmol/L*	<0.60 mEq/L *<0.30 mmol/L*
Pancreatic amylase[c]	≥1.1 to ≤1.5x ULN	>1.5 to ≤2.0x ULN	>2.0 to ≤5.0x ULN	>5.0x ULN
Phosphate, serum, low				
Adult and Pediatric >14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0–2.4 mg/dL *0.65–0.80 mmol/L*	1.0–1.9 mg/dL *0.32–0.64 mmol/L*	<1.00 mg/dL *<0.32 mmol/L*
Pediatric 1–14 years	3.0–3.5 mg/dL *0.97–1.13 mmol/L*	2.5–2.9 mg/dL *0.81–0.96 mmol/L*	1.5–2.4 mg/dL *0.48–0.80 mmol/L*	<1.50 mg/dL *<0.48 mmol/L*
Pediatric <1 year	3.5–4.5 mg/dL *1.13–1.45 mmol/L*	2.5–3.4 mg/dL *0.81–1.12 mmol/L*	1.5–2.4 mg/dL *0.48–0.80 mmol/L*	<1.50 mg/dL *<0.48 mmol/L*
Potassium, serum, high	5.6–6.0 mEq/L *5.6–6.0 mmol/L*	6.1–6.5 mEq/L *6.1–6.5 mmol/L*	6.6–7.0 mEq/L *6.6–7.0 mmol/L*	>7.0 mEq/L *>7.0 mmol/L*
Potassium, serum, low	3.0–3.4 mEq/L *3.0–3.4 mmol/L*	2.5–2.9 mEq/L *2.5–2.9 mmol/L*	2.0–2.4 mEq/L *2.0–2.4 mmol/L*	<2.0 mEq/L *<2.0 mmol/L*
Sodium, serum, high	146–150 mEq/L *146–150 mmol/L*	151–154 mEq/L *151–154 mmol/L*	155–159 mEq/L *155–159 mmol/L*	≥160 mEq/L *≥160 mmol/L*
Sodium, serum, low	130–135 mEq/L *130–135 mmol/L*	125–129 mEq/L *125–129 mmol/L*	121–124 mEq/L *121–124 mmol/L*	≤120 mEq/L *≤120 mmol/L*
Triglycerides (fasting)	NA	500–750 mg/dL *5.65–8.48 mmol/L*	751–1,200 mg/dL *8.49–13.56 mmol/L*	>1,200 mg/dL *>13.56 mmol/L*
Uric acid	7.5–10.0 mg/dL *0.45–0.59 mmol/L*	10.1–12.0 mg/dL *0.60–0.71 mmol/L*	12.1–15.0 mg/dL *0.72–0.89 mmol/L*	>15.0 mg/dL *>0.89 mmol/L*

[a] Values are for term infants.
[b] Use age- and sex-appropriate values (e.g., bilirubin), including preterm infants.
[c] Revised by the Sponsor.

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
URINALYSIS *Standard International Units are listed in italics*				
Hematuria (microscopic)	6–10 RBC/high power field (HPF)	>10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2–3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200–999 mg/24 h *0.200–0.999 g/d*	1,000–1,999 mg/24 h *1.000–1.999 g/d*	2,000–3,500 mg/24 h *2.000–3.500 g/d*	>3,500 mg/24 h *>3.500 g/d*
Pediatric >3 months – <10 years	201–499 mg/m2/24 h *0.201–0.499 g/d*	500–799 mg/m2/24 h *0.500–0.799 g/d*	800–1,000 mg/m2/24 h *0.800–1.000 g/d*	>1,000 mg/ m2/24 h *>1.000 sg/d*

7.3. Addendum 3: Visit Schedule for Cutaneous Reaction/Rash Follow-up

This visit schedule summarizes the visits and assessments to be performed in case of Cutaneous Reaction/Rash. At the investigator's discretion, additional visits and assessments can be performed.

For all trial visits, please perform assessments per "Unscheduled Visit in case of Cutaneous Reaction/Rash" CRFs and fax forms per instructions.

	Grade 1	Grade 2	Grade 3 or 4
Day 1[a]	Unscheduled trial visit for initial cutaneous reaction/rash evaluation and local lab assessment. Referral to a dermatologist is **OPTIONAL**. Biopsy is **OPTIONAL**. ARV medication may be continued.	Unscheduled trial visit for initial cutaneous reaction/rash evaluation and local lab assessment. Referral to a dermatologist is **OPTIONAL**. Biopsy is **OPTIONAL**. ARV medication may be continued.	Unscheduled trial visit for initial cutaneous reaction/rash evaluation and local lab assessment. Referral to a dermatologist and biopsy are **REQUIRED**, preferably within 24 hours. ARV medication MUST be discontinued.
Day 2	Follow-up visit, including local lab assessment.	Follow-up visit, including local lab assessment .	Follow-up visit, including local lab assessment .
Day 3	No cutaneous reaction/rash follow-up visit required. [b]	No cutaneous reaction/rash follow-up visit required. [b]	Follow-up visit.. Local lab AST/ALT assessment only if AST/ALT on Day 1 are ≥2x baseline value and/or ≥5x ULN, and/or in case of cutaneous reaction/rash progression.
Day 4	No cutaneous reaction/rash follow-up visit required. [b]	No cutaneous reaction/rash follow-up visit required. [b]	Follow-up visit. Local lab AST/ALT assessment only if AST/ALT on Day 1 are ≥2x baseline value and/or ≥5x ULN, and/or in case of cutaneous reaction/rash progression.
Day 5	No cutaneous reaction/rash follow--p visit required. [b]	No cutaneous reaction/rash follow-up visit required. [b]	Follow-up visit.Local lab AST/ALT assessment only if AST/ALT on Day 1 are ≥2x baseline value and/or ≥5x ULN, and/or in case of cutaneous reaction/rash progression.

Day 7	Follow-up visit, including local lab assessment[a].	Follow-up visit, including local lab assessment[b].	No cutaneous reaction/rash follow-up visit required.
Further Visits	If cutaneous reaction/rash unresolved after second follow-up visit (Day 7), further visits (including local lab assessments) at investigator's discretion.[b]	If cutaneous reaction/rash unresolved after second follow-up visit: – without AST/ALT increase: further visits (including local lab assessments) at investigator's discretion;[b] – with AST/ALT increase <2x baseline: weekly visits (including local lab).[b] – with AST/ALT increase ≥2x baseline but not reaching the criteria for grade 3 rash: weekly visits (including local lab assessments).[b]	Weekly visits until resolution/stabilization of cutaneous reaction and AST/ALT elevation, or more frequently at investigator's discretion. Local lab assessments if AST/ALT on Day 5 are ≥2x baseline value and ≥5x ULN.
Upon Rash Resolution/Stabilization	Complete Final Cutaneous Reaction/Rash Evaluation form.	Complete Final Cutaneous Reaction/Rash Evaluation form.	Complete Final Cutaneous Reaction/Rash Evaluation form.

[a] Day 1 of the rash-follow-up is the first day of investigator assessment and not the first day of rash as reported by the subject.

[b] In case cutaneous reaction/rash progresses to grade 3 or 4, start follow-up schedule for grade 3 or 4 cutaneous reaction/rashes as of Day 1 and conduct biopsy/referral to dermatologist. (Even if the subject was already referred to dermatologist in scope of grade 1 or 2 cutaneous reaction/rash.)

7.4. Addendum 4: Cardiovascular Safety – Abnormalities

ECG[a]

1) Adult >16 Years

All important abnormalities from the ECG readings will be reported.

The percentage of subjects with increases in QTc of <30, 30–60, or >60 ms from baseline will also be tabulated at each time point.

QTc (ms):

% Changes in QTc: increase of <30, 30–60 or >60ms from baseline

% Normal <450 & borderline &480 < prolonged <500 ≤ pathologically prolonged

QRS (ms):

% Normal <120 & abnormal

QTc change (ms):

% Normal <30 & borderline &60 < abnormal high

2) Pediatric &16 Years[b]

Prolonged QTc:

Grade 1: Asymptomatic, QTc interval 0.450–0.464 s

Grade 2: Asymptomatic, QTc interval 0.465–0479 s

Grade 3: Asymptomatic, QTc interval ! 0.480 s

Grade 4: Life-threatening consequences, e.g., Torsade de Pointes or other associated serious ventricular dysrhythmia

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[a] CPMP: Points to consider: The assessment of the potential for QTc interval prolongation by noncardiovascular medicinal products.

[b] See Addendum 2: DAIDS Table.

Vital Signs[c]

The following abnormalities will be defined for vital signs:

1) Adult >17 Years

Pulse (beats per minute):

% Abnormally high: ! 120 bpm

% Abnormally low: &50 bpm

DBP (mmHg):

% Abnormally high: Grade 1 or mild: >90 to <100 mmHg
Grade 2 or moderate: ! 100 to <110 mmHg
Grade 3 or severe: ! 110 mmHg

% Abnormally low: &50 mmHg

SBP (mmHg):

% Abnormally high: Grade 1 or mild: >140 to <160 mmHg
Grade 2 or moderate: ! 160 to <180 mmHg
Grade 3 or severe: ! 180 mmHg

% Abnormally low: &90 mmHg

2) Pediatric &17 Years

Pulse (beats per minute):

% abnormally high: ! 120 bpm

% abnormally low: &50 bpm

DBP and SBP (mmHg):

Grade 1: Not applicable

Grade 2: 91st-94th percentile adjusted for age, height, and gender (systolic and/or diastolic)

Grade 3: ! 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)

Grade 4: life-threatening consequences (e.g., malignant hypertension) OR hospitalization indicated (other than emergency room visit)

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[c] The DAIDS grading scale will be used to classify AEs related to hypotension and hypertension.

7.5. Addendum 5: HIV-Related Events or Outcomes in Adolescents and Adults (>13 Years Old)

7.5.1. Clinical categories[d]

The clinical categories of HIV infection are defined as follows.

7.5.1.1. Category A

Category A consists of 1 or more of the conditions listed below in an adolescent or adult (! 13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- % Asymptomatic HIV infection
- % Persistent generalized lymphadenopathy
- % Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

7.5.1.2. Category B (Symptomatic Non-AIDS Conditions)

Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C, and that meet at least 1 of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in clinical category B include, but are not limited to the following.

- % Bacillary angiomatosis
- % Candidiasis, oropharyngeal (thrush)
- % Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- % Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- % Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- % Hairy leukoplakia, oral
- % Herpes zoster (shingles), involving at least 2 distinct episodes or more than one dermatome;
- % Idiopathic thrombocytopenic purpura
- % Listeriosis
- % Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess;
- % Peripheral neuropathy

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[d] 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992; 41 (RR-17): 1-19.

For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.

The following list of other non-CDC HIV-associated conditions was compiled, as the CDC notes that Category B is not limited to events listed in the CDC 1993 definition.

- Aspergillosis
- Leishmaniasis
- Microsporidiosis
- Molluscum contagiosum
- Nocardiasis
- Thrombotic microangiopathy (haemolytic uremic syndrome/thrombotic thrombocytopenia purpura)

7.5.1.3. Category C (AIDS Indicator Conditions as Defined by Diagnostic or Presumptive Measures)

Category C includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C. Conditions in Category C include the following.

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, oesophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonitis, or oesophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, or brain
- *Mycobacterium avium* complex or *M. kansaii*, disseminated or extrapulmonary

- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia or *P. jiroveci* pneumonia
- Pneumonia, recurrent (more than one episode in one year period)
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

7.6. Addendum 6: HIV-Related Events or Outcomes in Children (<13 Years Old)

7.6.1. Clinical Categories[e]

The clinical categories for children with HIV infection are defined as follows.

7.6.1.1. Category N: Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

7.6.1.2. Category A: Mildly Symptomatic

Children with two or more of the conditions listed below but none of the conditions listed in Categories B and C.

- Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

7.6.1.3. Category B: Moderately Symptomatic

Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to:

- Anemia (<8 g/dL), neutropenia (<1.0x 10^9/L), or thrombocytopenia (<100x 10^9/L) persisting ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children >6 months of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month of age
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes Simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age

[e] CDC 1994 revised classification system for HIV infection in children. MMWR 1994; 43 (RR-12): 1-10.

- Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome
- Leimyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month of age
- Varicella, disseminated (complicated chickenpox)

7.6.1.4. Category C: Severely Symptomatic

Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicamia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)

- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least 1 of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings):
  - Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests;
  - Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age);
  - Acquired symmetric motor deficit manifested by 2 or more of the following: paresis, pathological reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi’s sarcoma
- Lymphoma, primary, in brain

- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunological phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Pneumocystis carinii pneumonia or P. jiroveci pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings:
  - Persistent weight loss >10% of baseline OR
  - Downward crossing of at least 2 of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age OR
  - >5th percentile on weight-for-height chart on 2 consecutive measurements, ≥30 days apart PLUS
    - Chronic diarrhea (i.e., at least 2 loose stools per day for ≥30 days) OR
    - Documented fever (for ≥30 days, intermittent or constant)

Definitive diagnosis: microscopy (histology or cytology); culture; antigen detection.

Presumptive diagnosis: characteristic clinical presentation, supported by investigations other than microscopy or culture and after exclusion of other causes in the differential diagnosis.

7.7. Addendum 7: Study Adherence Questionnaire for Children and Teenagers

Note: This questionnaire is a sample questionnaire. The site should always use the most recently provided version of the questionnaire.

TMC278-TiDP38-C213

Study Adherence Questionnaire for Children and Teenagers

To the investigator/trial personnel: please complete the following table and write the names, colour and type of the medicines that the child/teenager has been taking in the tables in question 1 and 8.

To be completed by the investigator/trial personnel:

Clinic Number:	Date of Birth:	Pediatric European Network For The Treatment of AIDS 11/ Trial Number:
Initials:	Date of Assessment:	
Week no. (please ring): baseline, 1, 2, 4, 8, 12, 16, 24, 32, 40, and 48	Completed by subject alone? *Yes* *No* If **no**, who else was involved? _____	If not completed: Not enough time Refusal Other *specify:* _____

To be completed by the subject

We know that it can be difficult taking medicines everyday. 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	Colour, 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 any one 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) 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:

7.8. Addendum 8: Study Adherence Questionnaire for Caregivers

TMC278-TiDP38-C213

Note: This questionnaire is a sample questionnaire. The site should always use the most recently provided version of the questionnaire.

Study Adherence Questionnaire for Carers

To the investigator/trial personnel: please complete the following table and write the names, colour and type of medicines that the child has been taking in the tables in question 3 and 8.

Clinic Number:	Date of Birth:	Pediatric European Network For The Treatment of AIDS 11/ Trial Number:
Initials:	Date of Assessment:	
Week no. (please ring): baseline, 1, 2, 4, 8, 12, 16, 24, 32, 40, and 48	Completed by 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 everyday. 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) What is your relationship to the child? Mother Father

Other (please specify) _____

2) A. Do you give antiretroviral medicines to your child? _____

B. Who else gives antiretroviral medicines to your child? _____

3) 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.			

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

None morning lunchtime/after school evening all

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

Easily quite easily with some difficulty with great difficulty

6) 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:*_____

7) 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? _____

8) 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

9) 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.			

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)?		
You were too depressed or unwell?		
You are fed up giving medicine?		

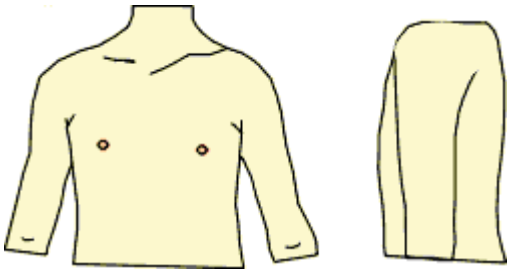
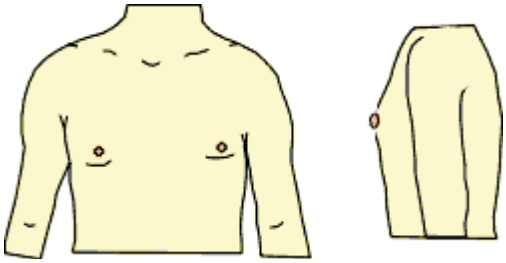
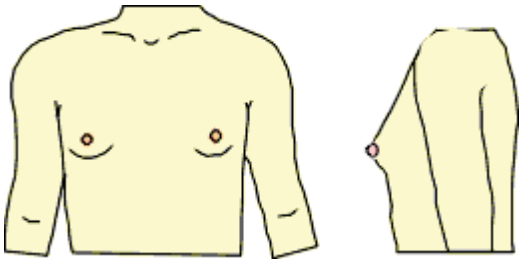
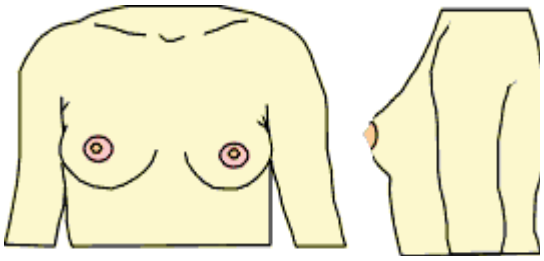
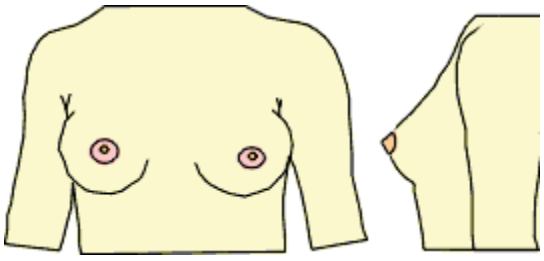
Further details or any other reason (please specify) :_____

Thank you for taking the time to fill out this form, please add any comments you have:

7.9. Addendum 9: Tanner Scales

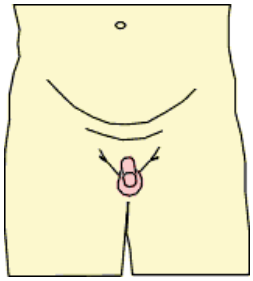
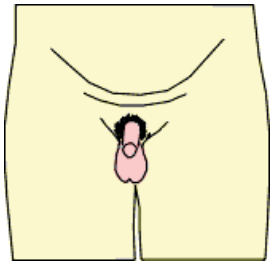
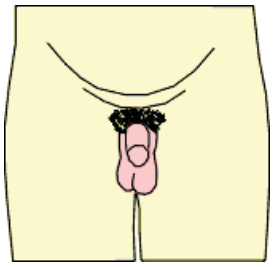
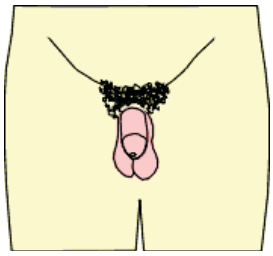
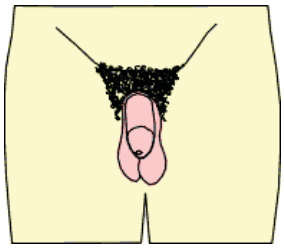
The Five Stages of Female Breast and Pubic Hair Development

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 for penis and testicle growth, Testicles become larger. Testicles between 4 and 6 millilitres 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 millilitres 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 1/2 inches long.	Pubic hair becomes adult type, but less.
5		Penis growth enters final stage. Average erect penis length 6 1/4 inches. 90% are 5-7 inches. Glans penis or head is fully developed. Testicles 16-27 millilitres in volume. Testicles are about 1-3/4 inches.	Pubic hair is thick spreading to medial thighs.

7.10. Addendum 10: Childhood Immunizations

Routine Childhood Immunizations:

Diphtheria, tetanus, pertussis, meningococcus C, mumps, and rubella.

Exceptions for Children With HIV Infection:

1. BCG. HIV positive individuals should not receive BCG vaccine; there have been reports of dissemination of BCG in HIV positive individuals.
2. Measles. Measles vaccine has been reported to cause fatal disease in one severely immunosuppressed HIV positive adult. Some experts do not recommend giving measles vaccine to HIV positive children with severe immunosupression (i.e., $CD4^+$ <15%).

   No harmful effects have been reported following live attenuated vaccines for mumps or rubella in HIV positive children.

3. Polio. The use of inactivated polio vaccine (IPV), which is safe in HIV-infected children, is recommended. The live, oral polio vaccine is not recommended.

   No harmful effects have been reported following oral, live attenuated polio vaccine in HIV positive children, although some experts recommend IPV be used for all HIV positive children.

4. Yellow fever. There is insufficient evidence as to the safety of Yellow fever vaccine in HIV positive people.

Additional Vaccines Can Be Safely Given When Needed:

Inactivated typhoid, inactivated cholera, hepatitis B, pneumococcal, rabies, hepatitis A, and meningococcal A+C vaccines.

Experts Recommendations:

Influenza vaccine annually
Pneumococcal vaccine (conjugate followed by polysacharide)

7.11. Addendum 11: Pharmacokinetic Modeling for Cohort 2 Dose Selection

As of Amendment 10

The modeling and simulation to define a bodyweight-adjusted RPV dose for children is an ongoing process, based on accumulating data over time. Recently the existing RPV population PK model for adults and adolescents was updated incorporating also the available RPV plasma concentration data from the ongoing subjects in Cohort 2 (≥6 to <12 years of age). The existing model was adjusted to better describe the RPV pediatric data by introducing allometric scaling (standard factor 0.75) on clearance and intercompartmental flow. Age was not found to be a significant covariate for the RPV model parameters.

With this revised model, RPV exposures across the whole bodyweight range were simulated and the following initial RPV dosing scheme was determined for newly enrolled subjects in Study C213 Cohort 2 and other ongoing RPV pediatric studies (TMC278HTX2002), regardless of age:

- 25 mg qd for children with a body weight of ≥25 kg;
- 15 mg qd for children with a body weight of ≥11 and <25 kg.

The simulations indicated that for subjects with a bodyweight ≥25 kg, a RPV dose of 25 mg qd can be used safely. CCI [redacted] the geometric mean AUC ratio for these pediatric subjects compared to adults, based on preliminary non-compartmental analysis of the 24 hour intensive PK visit, was 1.49 (<150% of adult value).

Children with bodyweight ≥11 and <25 kg will be dosed with an adjusted RPV dose of 15 mg qd. CCI [redacted] This dose is further supported by the fact that it is generally preferred, if safety allows, to dose antiretrovirals (ARVs) at the high rather than at the low end, from an efficacy perspective. In addition, the 0.75 allometric scaling factor may be a conservative estimate potentially overestimating the effect of bodyweight on the RPV PK, given the currently limited data for children with lower bodyweight.

The data and strategy were discussed with and supported by the IDMC for studies C213 and TMC278HTX2002.

Prior to Amendment 10

CCI

Figure 1: CCI

CCI

Table 1: CCI

CCI

Table 2: CCI

CCI

7.12. Addendum 12: Taste Assessment Form for Children

Note: This questionnaire is a sample questionnaire. The site should always use the most recently provided version of the questionnaire.

CHILDREN'S RILPIVIRINE TASTE TEST

Assessment time: _____ Date:_____

Site ID: _____

Subject ID:_____ Subject Initials: _____

ASK PARENT: How often did your child take the study medication rilpivirine dispersed in water?

- ☐ Most of the times (5 days or more)
- ☐ Some times (less than 5 days but more than one day)
- ☐ Rarely (only for one day or for one dose)

Tester Signature: _____

Tester Function: _____

Date:_____ **Site ID:**_____ **Subject ID:**_____ **Subject Initials:** _____

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. Please look at the pictures. How does this study medication taste to you when you drink it after mixing it with water?

READ SCALE AND POINT TO THE PICTURES (see appendix 1)
(If the child cannot convey their taste perception, parents can help the child)

- ☐ Really Good
- ☐ Pretty Good
- ☐ Okay
- ☐ Not good
- ☐ Terrible

Comment

2. Can you tell us what this study medication tasted like?

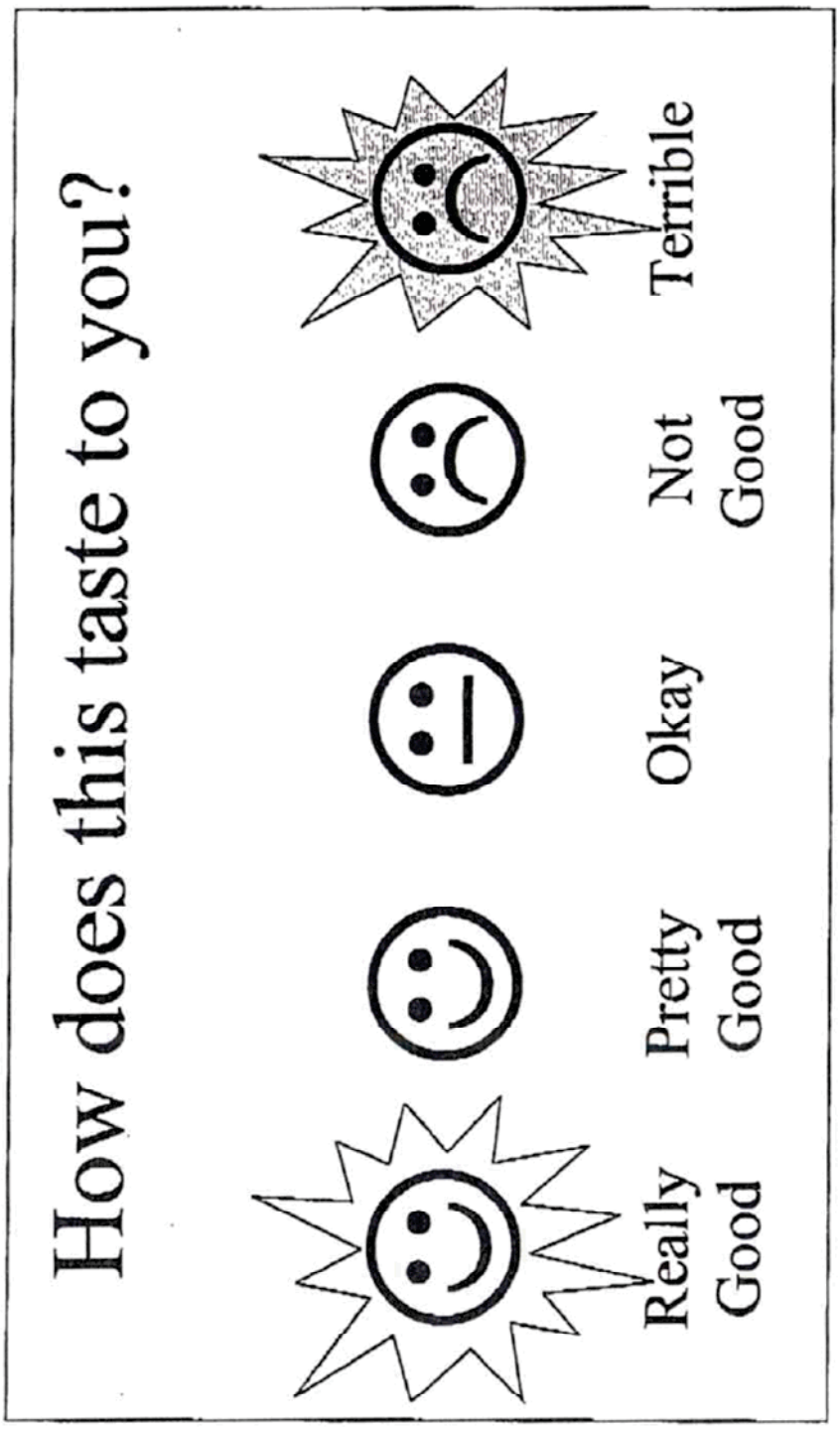
READ SCALE AND TICK THE BOX (see appendix 2)

- ☐ Tastes like water
- ☐ Tastes like _____

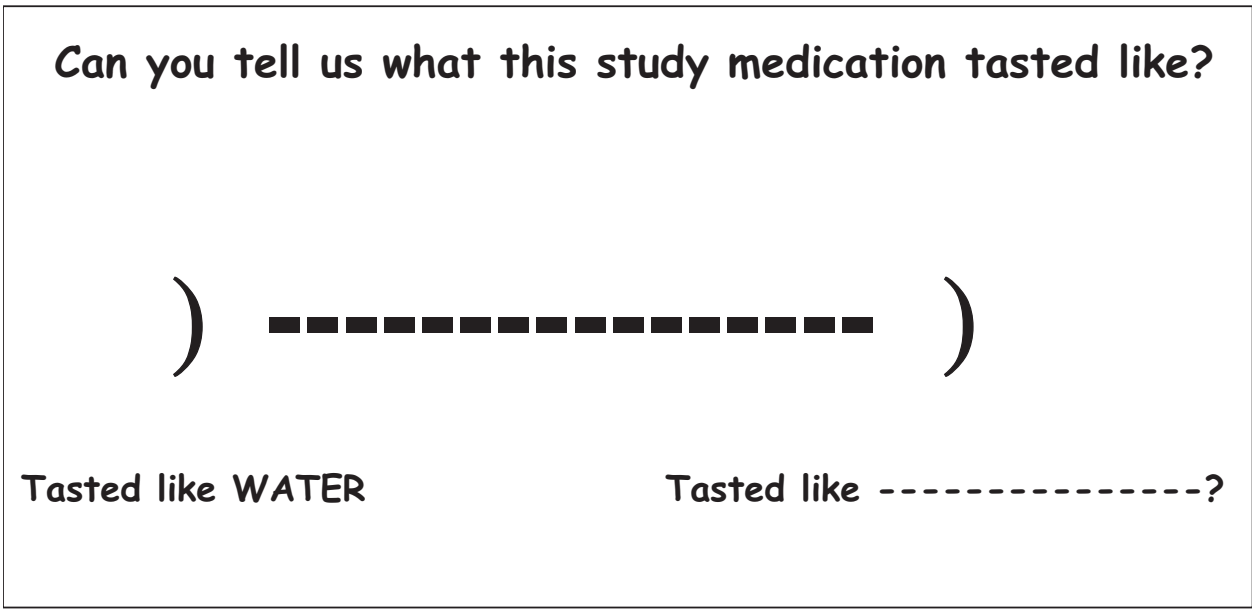
Comment

Thank you for participating in this taste evaluation process; you have been very helpful.

Appendix 1


How does this taste to you?
Really Good
Pretty Good
Okay
Not Good
Terrible

Appendix 2


Can you tell us what this study medication tasted like?
Tasted like WATER
Tasted like ----------?

PART 2. PROCEDURES

1. ADVERSE EVENTS

1.1. Definitions

ADVERSE EVENT

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonization - ICH E6; 1.2).

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.

SERIOUS ADVERSE EVENT

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject 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 (ICH E6; 1.50)
- Is a suspected transmission of any infectious agent via a medicinal product;
- Is Medically Important.

Note

- Medical and scientific judgment should be exercised in deciding whether expedited reporting is 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 subject or may require intervention to prevent 1 of the outcomes listed in the definition above. These events should usually be considered serious.

- Hospitalizations that were planned prior to 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 (see also Section 1.4).
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period; this will not be considered as a SAE.

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 Investigator's Brochure.

LIFE-THREATENING

Any event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

ASSOCIATED WITH THE USE OF THE DRUG

An AE is considered associated with the use of the drug if the attribution is possible, probable or very likely.

1.2. Attribution Definitions

NOT RELATED

An AE which is not related to the use of the drug.

DOUBTFUL

An AE for which an alternative explanation is more likely, e.g., concomitant drug(s) or concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

POSSIBLE

An AE which might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s) or concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

PROBABLE

An AE which might be due to the use of the drug. The relationship in time is suggestive, e.g., confirmed by dechallenge. An alternative explanation is less likely, e.g., concomitant drug(s) or concomitant disease(s).

VERY LIKELY

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

1.3. HIV-Related Events or Outcomes

The events or outcomes listed in the classification list (see Part I, Addendum 5: HIV-Related Events or Outcomes in Adolescents and Adults and Addendum 6: HIV-Related Events or Outcomes in Children) will be recorded as HIV-related events on the eCRF. These events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormalities that can be linked to any of these events or outcomes, are not to be reported as an AE.

1.4. Reporting of AEs and HIV-Related Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, 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.

AEs and HIV-related events will be collected from the signing of the ICF until completion of the subject's last trial-related procedure (which may include contact for follow-up of safety). Occurrence of AEs and HIV-related events will be reported in the AE and HIV-Related Events sections of the eCRF, respectively.

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

All AEs still ongoing at the end of the treatment will be followed until satisfactory resolution (i.e., 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 trial will be followed as agreed between the Sponsor and investigator.

Certain long-term AEs of ARTcannot 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.

SAEs occurring within the clinical trial (between signing of the ICF and last follow-up visit) and those spontaneously reported to the investigator within 30 days after the last dose of study drug must be reported using the Serious Adverse Event Form. The Sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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 a SAE, the start date of the SAE must be the same as the start date of the worsened AE.

The cause of death of a subject in a clinical trial, whether the event is expected or associated with the investigational agent, is a SAE.

Information regarding SAEs will be transmitted to the Sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the trial site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the trial, or that have not resolved upon discontinuation of the subject's participation in the trial, 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 drug or to factors unrelated to trial conduct
- It becomes unlikely that any additional information can be obtained (subject 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 subject's participation in a trial must be reported as an SAE, except hospitalizations for the following:

- Surgery or procedure planned before entry into the trial (must be documented in the eCRF). 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.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the Sponsor by the trial-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the trial must be promptly withdrawn from the trial and discontinue further trial treatment.

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

The Sponsor or its representatives will assume responsibility for appropriate reporting of AEs to 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 (IEC)/Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

Special reporting situations

Safety events of interest on a Sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Inadvertent or accidental exposure to a Sponsor study drug
- Medication error involving a Sponsor study drug (with or without subject/patient exposure to the Sponsor study drug, e.g., name confusion)

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

2. TRIAL CLOSURE CONSIDERATIONS

2.1. Trial Completion

The trial is considered completed with the last trial visit for the last subject participating in the trial. The final data from the trial site will be sent to the Sponsor (or designee) after completion of the final subject visit at that trial site, in the time frame specified in the Clinical Trial Agreement.

2.2. Trial Termination

The Sponsor reserves the right to close an investigational site or terminate the trial at any time for any reason. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

Reasons for the closure of an investigational site or termination of a trial by the Sponsor may include but are not limited to:

- Successful completion of the trial at the center
- The overall required number of subjects for the trial has been recruited
- Failure of the investigator to comply with the protocol, ICH-Good Clincial Practice (GCP) guidelines or local requirements
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

3. TRIAL MATERIALS

3.1. Investigational Products

The investigator acknowledges that the drug supplies are investigational and as such must be handled strictly in accordance with the protocol and the container label. Supplies must be retained in a limited access area and under the appropriate environmental conditions as specified on delivery. Supplies should be dispensed under the supervision of the investigator or subinvestigator, or by a hospital pharmacist. Local regulations should be adhered to.

It is the investigator's responsibility to ensure that subjects or those held to be responsible for subjects, return their medication (including empty packages, e.g., empty blisters). Returned supplies must not be dispensed again, even not to the same subject. Each time medication is dispensed to or returned by the subject, this must be documented on the Drug Accountability Form. Whenever a subject brings his/her medication to the site for pill count this is not seen as a

return of supplies. Unused medication and medication returned by the subject must be available for verification by the monitor.

All used and unused study drug will be returned to the Sponsor or will be passed over for destruction on-site (conform local regulations), or by an authorized destruction unit after authorization by the Sponsor. This will be documented on the Drug Return Form and a destruction certificate or on the Investigational Product Destruction Form, if applicable.

3.2. Trial Documents

For Cohort 1 the following documents must be provided to the Sponsor or representatives before shipment of RPV to the trial center.

- A signed and dated protocol and amendment(s), if any.
- A copy of the signed and dated written IEC/IRB approval specifying the documents being approved: the protocol, amendments, ICF, Informed Assent Form, any other written information provided to the subject, if applicable, subject compensation programs and subject recruitment materials. This approval must clearly identify the trial by protocol title and trial number and must be signed by the chairman or authorized designee.
- Regulatory authority approval or notification, if required.
- Documentation on which the assessment of the investigator's qualifications was based (e.g., curriculum vitae).

For Cohort 2, in addition to the items mentioned above also the items below must be provided to the Sponsor or representatives before shipment of RPV to the trial center:

- 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 trial-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 trial.
- Signed and dated statement of investigator (e.g., Form FDA 1572), if applicable.
- 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.

For both cohorts, the following documents must be provided to the Sponsor or representatives prior to enrollment of the first subject (unless it was already required to be provided before shipment of RPV to the trial center [see above for Cohort 2]).

- The names of the current members or composition of the IEC/IRB and their position in the health-care institution or their credentials. In case the (sub)investigator is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the voting for the trial.
- Completed Investigator Financial Disclosure Forms from the investigator and all subinvestigators.
- Signed and dated trial agreement, if applicable.
- Signed and dated financial agreement.
- Documentation on which the assessment of the subinvestigators' qualifications was based (e.g., curriculum vitae).
- Name and address of any local laboratory conducting tests for the trial and current laboratory normal ranges for all tests required by the protocol that will be performed.
- Laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

For Cohort 2, the following documents must also be provided:

- Completed Site Signature Log–Delegation of Responsibilities (SSL-DoR) (FRM-15505), mandatory task-related training, and completed Investigational Staff Training Documentation (ISTD) (FRM-15506) for Principal Investigator, Head Pharmacist (if applicable) and other identified key investigational staff (e.g., Rater, Trial Coordinator, if applicable).

The investigator will be provided with the following supplies:

- Investigator's Brochure
- Pharmacy manual/trial site investigational product manual
- Laboratory manual
- Questionnaires and user manuals
- Electronic Data Capture (EDC) manual
- Central ECG machine and ECG manual
- Any other manual, as applicable
- Sample ICF and assent form
- Subject diaries
- Contact Information page(s)
- Subject Participation Card
- Recruitment and enrollment tools

3.3. Participation Cards

Cohort 1: Adolescents Aged ≥12 to <18 Years

If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-subjects), they must be provided with a Subject Participation Card indicating the name of the investigational product, the trial number, the investigator's name and a 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

Cohort 2: Children Aged ≥6 to <12 Years

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

- Trial number
- Statement, in the local language(s), that the subject is participating in a clinical trial
- 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
- Subject number

The wallet (trial) card has to be in the subject's local language and may also include a translation in an additional language, as appropriate.

3.4. Source Data

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Trial identification
- Trial discussed and date of informed consent
- Dates of all visits
- Results of efficacy parameters, as required by the protocol
- Drug receipt/dispension/return records, study drug administration information
- Record of all AEs and follow-up of AEs
- Concomitant medication

- Date of trial completion and reason for early discontinuation of study drug or withdrawal from the trial, if applicable

In addition, the author of an entry in the source documents should be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial and will be described in the monitoring guidelines (or other equivalent document).

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

- Race
- History of smoking
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

Subject- and investigator-completed scales, assessments, and diaries designated by the Sponsor will be recorded and will be considered source data. Information from the diary, provided to subjects, will be reviewed by the investigator or designee before data management transcribes the data into the relevant parts of the eCRF. Refer to the CRF Completion Guideline for more details about how the source data is transferred to the eCRF.

The minimum source documentation requirements for Section 6.2.2, Inclusion Criteria and Section 6.2.3, 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 subject interview or other protocol required assessment (e.g., physical examination, laboratory assessment) and documented in the source documents.

3.5. Electronic Case Report Forms

Case report forms are provided for each subject in electronic format.

Electronic Data Capture will be used for this trial, meaning that all data will be entered in eCRF at the investigational site.

All data must be entered in English.

The eCRFs should always reflect the latest observations on the subjects participating in the trial. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid interobserver variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy/safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off the clinical data.

The monitor will review the eCRFs, evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance.

If additional corrections are needed, the responsible monitor or data manger will raise a query in the EDC application. The appropriate investigational staff will answer queries sent to the investigator. This will be audit-trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

3.6. Subject Identification Code List & Subject Screening and Enrollment Log

In order to permit easy identification of the individual subject during and after the trial, the investigator is responsible for keeping an updated Subject Identification Code List or subject identification and enrollment log. The monitor will review this document for completeness. However, in order to ensure subject confidentiality, this document will remain at the center and no copy will be made. All reports and communications relating to the trial will identify subjects by subject identification and date of birth. In cases where the subject is not enrolled into the trial, the date seen and date of birth will be used.

A Subject Screening and Enrollment Log on all subjects who were seen to determine eligibility for inclusion in the trial also has to be completed by the investigator.

3.7. Archiving

The investigator shall maintain the trial documents as specified in "Essential Documents for the Conduct of a Clinical Trial" (ICH E6; 8.2-8.4) and as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents should 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however, if required by the applicable regulatory requirements.

It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained a written approval of the Sponsor.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, 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.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the ICF.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the trial.

3.8. 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 subjects, 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) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor

representative (see Contact Information page(s) provided separately). 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

3.9. Monitoring

The Sponsor will use a combination of monitoring techniques to monitor this trial.

The Sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial site visit log that will be kept at the trial 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 eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and trial-site personnel and are accessible for verification by the Sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel.

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

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

Central monitoring will take place for data identified by the Sponsor as requiring central review.

4. CONFIDENTIALITY

All information concerning the product and the Sponsor’s operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the Sponsor and not previously published) is considered confidential by the Sponsor and should not be disclosed by the investigator to any third party without the Sponsor’s prior written approval. The investigator agrees to use this information only in accomplishing the trial and will not use it for other purposes.

5. REPORTING AND PUBLICATION

5.1. Reporting

The Sponsor will create a Development Safety Update Report (DSUR) and Line Listings in accordance with the ICH guideline E2F with a data-lock date of 20 May. This trial TMC278-TiDP38-C213 will be included in the first DSUR produced after approval of this protocol, which may be less than 1-year's time from this particular trial approval date, and in all subsequent DSURs, as appropriate, until trial closure.

The results of the trial will be reported in clinical study reports per Cohort. A summary of the final report will be provided to the investigators, to the applicable regulatory authorities, and IECs/IRBs, if required by the applicable regulatory requirements, within 1 year after end of trial. If deemed appropriate, additional interim clinical study reports will be created to describe information from other analyses (e.g., primary analysis, interim analysis).

One investigator will be appointed for signing off the final clinical study report. The selection of this investigator will be determined by the recruitment performance and specific expertise related to the nature and the key assessment parameter(s).

5.2. Use of Information and Publication

All information, including but not limited to information regarding RPV or the Sponsor's operations (e.g., 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 trial, 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 trial, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the trial 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 trial.

Results of analyses performed after the clinical study reports have been issued will be reported in a separate report and will not require a revision of the clinical study report. Trial subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) 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 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 trial site-specific data after the primary data are published. If an investigator wishes to publish information from the trial, 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. In the event that 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 trial designs and subtrial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the Sponsor confirms there will be no multicenter trial publication. Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of clinical studies and disclosure of results

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

6. AUTHORITIES/ETHICS

6.1. Regulatory Authorities

This trial will be submitted to the local regulatory authority for approval or notification whichever is applicable. The trial will only be undertaken in compliance with the local regulatory requirements.

6.2. Independent Ethics Committee/Institutional Review Board

Before the start of the trial, the investigator (or Sponsor where required) 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 subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials

- Information on compensation for trial-related injuries or payment to subjects for participation in the trial, 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 subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This trial can only be undertaken after full approval of the protocol, informed consent, any other written information given to subjects, and subject recruitment materials has been obtained from the IEC/IRB. This document must be dated and clearly identify the trial and the documents being approved, including the subject compensation programs.

During the trial the following documents will be sent to the IEC/IRB for their review:

- Changes to the Investigator's Brochure
- Reports of AEs that are serious, unlisted and associated with the investigational drug
- DSUR and Line Listings
- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or trial conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the Sponsor
- Revisions to compensation for trial-related injuries or payment to subjects for participation in the trial, if applicable
- Summaries of the status of the trial at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- New information that may adversely affect the safety of the subjects or the conduct of the trial
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the trial at the site
- Any other requirements of the IEC/IRB

Substantial amendments and applicable ICF revisions must promptly be submitted to the IEC/IRB for review and approval prior to implementation of the change(s), except when necessary to eliminate an immediate hazard to the trial subjects.

The IEC/IRB is responsible for continuous review of the trial. At least once a year, the investigator will provide the IEC/IRB with a progress report to allow review of the trial. Additional progress reports should be provided if required by the IEC/IRB.

These requests and (re)approvals, if applicable, should be documented in writing.

At the end of the trial, the investigator (or Sponsor where required) will notify the IEC/IRB about the trial completion.

6.3. ICH-GCP Guidelines

This trial will be conducted in accordance with the current ICH-GCP Guidelines.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

6.4. Subject Information and Informed Consent

General

Prior to entry in the trial, the investigator or a person designated by the investigator must explain to potential subjects and/or their parent(s) or legally authorized representative(s) the trial and the implications of participation (the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail). During the trial, subjects and/or their parent(s) or legally authorized representative(s) will be given any new information that may affect their decision to continue participation. Subjects will be informed that their participation is voluntary and that they may withdraw from the trial at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. They will be informed that choosing not to participate or to withdraw from the trial will not have an impact on the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part in this trial. Finally, they will be told that their records may be accessed by the IEC/IRB, competent authorities and authorized representatives of the Sponsor or the contract research organization (CRO) without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the ICF, the subject or their parent(s)/legally authorized representative(s) are authorizing such access, and agree to allow his or her trial physician to recontact the subject and/or their parent(s) or legally authorized representative(s) for the purpose of obtaining consent for additional safety evaluations, if needed. Only subjects and/or their parent(s) or legally authorized representative(s) who are fully able to understand the risks, benefits, and potential adverse events of the trial, and provide their consent/assent voluntarily will be enrolled.

The ICF(s) must be signed before performance of any trial-related activity. The ICF(s) and assent form(s) that are used must be approved by both the Sponsor and by the reviewing

IEC/IRB and be in a language that the subject and their parent(s) or legally authorized representative(s) can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

If a subject and his/her parent or legally authorized representative are unable to read, an impartial witness must be present during the entire informed consent discussion. The signature of the impartial witness will certify the subject's or parent's or legally authorized representative's consent. The subject and/or their parent(s) or legally authorized representative(s) will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the trial, consent should be appropriately recorded by means of either the subject's or his or her parent's or legally authorized representative's personally dated signature or by the signature of an independent witness who certifies the subject's or his or her parent's or legally authorized representative's consent in writing. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

Any information relevant to the subject's willingness to participate in the trial will be provided to the subject and/or their parent(s) or legally authorized representative(s) in a timely manner by means of an updated ICF. This amended ICF will be signed by either the subject or their parent(s) or legally authorized representative(s) and the investigator to document the willingness of the subject to continue with the trial. This signed and dated amended version will be filed together with the initial signed and dated ICF.

Pediatric subjects

The special vulnerability of children requires specific measures in the informed consent process in order to safeguard their interests and to protect them from harm.

As a rule, a pediatric subject is legally unable to provide informed consent. Therefore children are dependent on their parent(s)/legal guardian to assume responsibility for their participation in the clinical trial. While children are legally incapable of giving informed consent, they nevertheless may possess the ability to assent or to dissent from participation. Out of respect for children as developing persons, children will be asked whether or not they wish to participate in the research, after having been informed about the trial 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. Where appropriate, participants should assent to enroll in a trial (age of assent is to be determined by IEC/IRB or to be consistent with local legal requirements). The parent(s)/legal guardian will be responsible for the actual informed consent, while the child will be asked to assent. Minors who assent to a trial and later withdraw that assent should not be maintained in the trial against their will, even if their parents still want them to participate.

The following information forms (including consent / assent form) will be used by the investigational staff:

- Parent / legal guardian and adolescent information sheet and consent form
- Children information sheet and assent form

The way these forms are composed and used will be in accordance with local laws and regulations (e.g., the age at which adolescents are legally declared 'mature' may differ from country to country, and in case children can not write their names, drawing for example a smiley face to assent is allowed practice in some countries).

All applicable forms will be submitted for review and approval to IECs/IRBs.

If local regulations allow, the investigator/trial nurse or social worker could also consider having a private session with the subject to address sensitive issues related to alcohol use, sexual activity, drug screen and any other.

6.5. Privacy of Personal Data

The processing of personal data in pursuit of this trial will be limited to those data that are reasonably necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this trial. These data will be processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor or its representatives whose responsibilities require access to personal data are obliged to keep the identity of trial subjects confidential. 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. This confidentiality will be maintained throughout the complete data processing. Trial subjects will be entitled to request confirmation of the existence of personal data held by the Sponsor and will have the right to rectify erroneous or inaccurate data. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the trial, and the applicable laws and regulations.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-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.

6.6. Country Selection

This trial will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product.

7. FINANCING AND INSURANCE

7.1. Financial Disclosure

The disclosed financial interest of the investigator must be collected before enrollment of the first subject. The investigator should promptly update this information if any relevant changes occur up to 1 year following trial completion.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any investigator(s) added as investigational staff must complete the Investigator Financial Disclosure Form at the beginning of their participation in the trial. For any investigator(s) leaving the site prior to trial completion, an Investigator Financial Disclosure Form should be obtained in case of updates at the end of their participation.

7.2. Indemnification

The Sponsor undertakes to indemnify and hold harmless the investigator and his/her medical staff from any claim, demand or cost arising from the activities to be carried out in compliance with the protocol, as further specified in the Clinical Trial Agreement.

7.3. Insurance

Sponsor ensures that an appropriate liability insurance is available covering injuries arising from the participation of the trial subject in this trial, as further specified in the Informed Consent and the Clinical Trial Agreement.

8. DATA QUALITY CONTROL/ASSURANCE

The trial will be monitored by the Sponsor or representatives according to the current Standard Operating Procedure for the monitoring of clinical trials.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial-site personnel before the trial, and periodic monitoring visits by the Sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Shortly before the trial starts, the monitor will meet with the investigator and all staff involved to review the procedures regarding trial conduct and recording the data into the eCRF system. During the trial, the investigator shall permit the Site Manager to verify the progress of the trial at the center as frequently as necessary. The Sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor After upload of the data into the trial database they will be verified for accuracy and consistency with the data sources. The investigator shall make the electronic data screens available, provide missing or corrected data, and will correct the data in the eCRF system. Personal information will be treated as strictly confidential and will not be made publicly available.

The Sponsor will ensure that appropriate Quality Control (QC) steps are included into the different clinical processes to guarantee adequate protection of the trial subjects and quality of the data.

An independent Quality Assurance (QA) department, regulatory authorities and/or IECs/IRBs may review this trial. This implies that auditors/inspectors will have the right to inspect the trial center(s) at any time during and/or after completion of the trial and will have access to source documents, including the subject's file. By participating in this trial, investigators agree to this requirement. The investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the Sponsor or its designees.

The investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection (both announced and unannounced).

For any data transfer, measures will be undertaken to protect subject data handed over against disclosure to unauthorized third parties and subject confidentiality will be maintained at all times.

9. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., 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 subjects, 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.

9.1. Procedures

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

If the defect is combined with an SAE, the trial-site personnel must report the PQC to the Sponsor according to the SAE reporting timelines (refer to Section 1.4). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

9.2. Contacting Sponsor Regarding Product Quality

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

SIGNATURE PAGE

Global Medical Leader/Trial Physician:

This document has been reviewed and approved by the Sponsor in order to ensure compliance with Good Clinical Practices.

Name: PPD

Affiliation: Janssen Research & Development

See appended electronic signature page

Investigator:

The trial will be performed in compliance with Good Clinical Practices, including the archiving of essential documents.

Name:

Affiliation:

Signature & Date:

SIGNATURES

Signed by	Date	Justification
PPD	03Feb2020, 15:38:43 PM, UTC	Document Approval

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

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

Protocol TMC278-TiDP38-C213; Phase II

TMC278 rilpivirine

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF THE PROTOCOL EDMS-ERI-102141585

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2008-001696-30

Status: Approved
Date: 3 June 2020
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-60771 v1.0

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

COVID-19 APPENDIX

GENERAL GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by patients and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related patient management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of patients and site staff and to maintain oversight of delegated trial activities. If, at any time, a patient's safety is considered to be at risk, study drug will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, patients will be interviewed to collect safety data. Sampling for efficacy endpoint assessments should be conducted and stored on-site or performed locally in case sample shipments to the central laboratory are disrupted. Patients will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for patients, including follow up. Modifications to protocol-required assessments may be permitted after consultation with the patient, investigator, and the sponsor. Missed assessments/visits will be documented as protocol deviations with the prefix "COVID-19 related". Discontinuation of study drug and withdrawal from the study should be documented with the prefix "COVID-19 related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a patient has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study drug and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

The following emergency provisions are meant to ensure patient safety on study while site capabilities are compromised by COVID-19 related restrictions. Remote medical consultation and alternatives to study drug dispensing, administration, and clinical laboratory assessments may allow continued study participation for patients in this trial.

As local restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible and in accordance with any country-specific regulatory requirements.

1. Study visits and procedures

- The feasibility for each patient to return for scheduled visits should be evaluated based on the site's local, regional, and institutional situation.

- Sites with full capacity to conduct study visits in-person at the study site should continue to do so in full compliance with the protocol.

- Patients who miss a scheduled visit may be rescheduled at the next appropriate opportunity. The patient's situation should be evaluated on a case-by-case basis and the study responsible physician should be contacted for discussion and decision. Every effort will be made to keep patients on treatment if it is in their best interest.

- Adherence counseling regarding the importance of maintaining the RPV-based ARV regimen should be conducted for all study patients at each study visit, or via telephone as applicable, if visits cannot be performed.

- In addition, patients may have tele-health visits conducted by qualified site personnel via phone or video conversation as per local regulation. Assessments may include review of adverse events, concomitant medications and study intervention accountability. Patients will also be questioned regarding general health status to fulfill any physical examination requirement. If questionnaires need to be performed during tele-health visits, a mitigation plan for collecting responses to questionnaires will be installed.

- If blood samples cannot be sent in real-time to the central laboratory (Covance) for central assessments, the study site should verify if the sample can be stored locally per Covance instructions, until shipping can be performed. If real-time laboratory results for safety and/or efficacy are considered needed by the investigator, a local laboratory can be used.

2. Dispensation of RPV

- The dispensation of RPV in the study is done at certain visits specified in the protocol with some flexibility in the planning of the visits allowed. Given the exceptional nature of the COVID-19 pandemic, and the potential that study patients may not be able to attend site visits within the study-specified visit windows, it is recommended to dispense an additional

kit of RPV, if required, to ensure that patients have sufficient supply of RPV. A table for reference can be found in Addendum 1 with visit windows and number of RPV kits which can be dispensed.

! The patients should bring all available study drug at their study visits. The patients should be instructed to keep the new kit as a buffer, and open only one kit at a time. The buffer kit should be re-dispensed at the following visit to the same patient if the kit is unopened. Re-dispensation of an unopened kit will be considered a minor protocol deviation and needs to be recorded in the source document and eCRF with the prefix "COVID-19 related" added.

3. Exposure to coronavirus/development of COVID-19.

In the event a patient develops a SARS-CoV-2 infection, local and institutional guidelines will be followed. The event will be reported to the sponsor and usual Adverse Event/SAE reporting requirements will be implemented.

4. Monitoring by the sponsor

Depending on local restrictions, routine on-site monitoring visits may be postponed. The site monitor may set up remote visits in accordance with site and local requirements instead. Additional monitoring visits may be needed in the future to catch up on monitoring activities that can only be performed on-site.

5. **Site audits**

During the COVID-19 pandemic and at the impacted sites, study site GCP audits with direct impact/engagement from the investigator and study site personnel will not be conducted, to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement if possible.

Addendum 1: Dispensing Table

25mg dose. Unit: Dose pack of 34 tablets of 25mg

Visit	Duration to next visit (weeks)	Visit window	Number of pack(s) to dispense NO visit window	Number of pack(s) to dispense PLUS visit window
Day 1	4	0	1	2
Week 1	---	2 day	0	0
Week 2	---	2 day	0	0
Week 4	4	1 week	1	2
Week 8	4	1 week	1	2
Week 12	4	1 week	1	2
Week 16	8	1 week	2	2
Week 24	8	1 week	2	2
Week 32	8	1 week	2	2
Week 40	8	1 week	2	2
Week 48	12	1 week	3	3
Week 60	12	1 week	3	3
Week 72	12	1 week	3	3
Week 84	12	1 week	3	3
Week 96	12	1 week	3	3
Week 108	12	1 week	3	3
Week 120	12	1 week	3	3
Week 132	12	1 week	3	3
Week 144	12	1 week	3	3
Week 156	12	1 week	3	3
Week 168	12	1 week	3	3
Week 180	12	1 week	3	3
Week 192	12	1 week	3	3
Week 204	12	1 week	3	3
Week 216	12	1 week	3	3
Week 228	12	1 week	3	3
Week 240	---	1 week	0	0

15mg dose. Unit: Bottle of 65 tablets of 2.5mg

Visit	Duration to next visit (weeks)	Visit window	Number of bottle(s) to dispense NO visit window	Number of bottle(s) to dispense PLUS visit window
Day 1	4	0	3	3
Week 1	---	2 day	0	0
Week 2	---	2 day	0	0
Week 4	4	1 week	3	4
Week 8	4	1 week	3	4
Week 12	4	1 week	3	4
Week 16	8	1 week	6	6
Week 24	8	1 week	6	6
Week 32	8	1 week	6	6
Week 40	8	1 week	6	6
Week 48	8	1 week	0	0

15mg dose. Unit: Dose pack of 48 tablets of 2.5mg

Visit	Duration to next visit (weeks)	Visit window	Number of pack(s) to dispense NO visit window	Number of pack(s) to dispense PLUS visit window
Day 1	4	0	4	4
Week 1	---	2 day	0	0
Week 2	---	2 day	0	0
Week 4	4	1 week	4	5
Week 8	4	1 week	4	5
Week 12	4	1 week	4	5
Week 16	8	1 week	7	8
Week 24	8	1 week	7	8
Week 32	8	1 week	7	8
Week 40	8	1 week	7	8
Week 48	8	1 week	0	0

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: [electronic signature appended at the end of the protocol] Date: _____

(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.

Signature

User	Date	Reason
PPD	03-Jun-2020 16:31:27 (GMT)	Document Approval