Integrated Review

Table 1. Administrative Application Information (NDA 202022 Supplement 20)

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	202022
Supplement number	20
Priority or standard	Priority
Submit date(s)*	7/25/2023
Received date(s)	7/25/2023
PDUFA goal date	1/25/2024
Division/office	Division of Antivirals (DAV)
Review completion date	3/1/2024
Established/proper name	Rilpivirine
(Proposed) proprietary name	Edurant
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1)
Code name	Not applicable
Applicant	Janssen, Products, L.P.
Dosage form(s)/formulation(s)	Tablet
Dosing regimen	25 mg once daily
Applicant proposed indication(s)/ population(s)	Treatment of HIV-1 infection in treatment-naïve pediatric patients weighing at least 25 kg to <35 kg
Proposed SNOMED indication	86406008 |Human immunodeficiency virus infection (disorder)|
Regulatory action	**Approval**
Approved dosage (if applicable)	25 mg once daily
Approved indication(s)/ population(s) (if applicable)	Treatment of HIV-1 infection in treatment-naïve pediatric patients weighing at least 25 kg
Approved SNOMED term for indication (if applicable)	40780007: |Human immunodeficiency virus I infection (disorder)|

Table 2. Administrative Application Information (NDA 202022 Supplement 22)

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	202022
Supplement number	22
Priority or standard	Priority
Submit date(s)*	7/25/2023
Received date(s)	7/25/2023
PDUFA goal date	1/25/2024
Division/office	Division of Antivirals (DAV)
Review completion date	3/1/2024
Established/proper name	Rilpivirine
(Proposed) proprietary name	Edurant
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1)
Code name	Not applicable
Applicant	Janssen, Products, L.P.
Dosage form(s)/formulation(s)	Tablet
Dosing regimen	25 mg once daily
Applicant proposed indication(s)/ population(s)	Treatment of HIV-1 infection in virologically-suppressed pediatric patients weighing at least 25 kg to <35 kg
Proposed SNOMED indication	86406008 |Human immunodeficiency virus infection (disorder)|
Regulatory action	**Approval**
Approved dosage (if applicable)	25 mg once daily
Approved indication(s)/ population(s) (if applicable)	Treatment of HIV-1 infection in treatment-naïve pediatric patients weighing at least 25 kg
Approved SNOMED term for indication (if applicable)	40780007: |Human immunodeficiency virus I infection (disorder)|

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Table 3. Administrative Application Information (NDA 219016 Original-1)

Category	Application Information
Application type	NDA
Application number(s)	219016 Original-1
Priority or standard	Priority
Submit date(s)*	9/15/2023
Received date(s)	9/15/2023
PDUFA goal date	3/15/2024
Division/office	Division of Antivirals (DAV)
Review completion date	3/1/2024
Established/proper name	Rilpivirine
(Proposed) proprietary name	Edurant PED
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1)
Code name	Not applicable
Applicant	Janssen
Dosage form(s)/formulation(s)	Tablets, for oral suspension
Dosing regimen	Dose differs by weight band; see review and labeling for full details.
Applicant proposed indication(s)/ population(s)	Treatment of HIV-1 infection in treatment-naïve pediatric patients ≥2 years of age and weighing at least 10 kg and less than 25 kg
Proposed SNOMED indication	86406008 |Human immunodeficiency virus infection (disorder)|
Regulatory action	**Approval**
Approved dosage (if applicable)	Dose differs by weight band; see review and label for full details
Approved indication(s)/ population(s) (if applicable)	Treatment of HIV-1 infection in treatment-naïve pediatric patients ≥2 years of age and weighing at least 14 kg and less than 25 kg
Approved SNOMED term for indication (if applicable)	40780007: |Human immunodeficiency virus I infection (disorder)|

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Glossary

ABC	abacavir
ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
AZT	zidovudine
CR	Complete Response
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration (also, the *Agency*)
FTC	emtricitabine
GOF	goodness of fit
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
IDMC	independent data monitoring committee
INSTI	Integrase strand transfer inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MS	millisecond(s)
MTCT	mother-to-child transmission
NA	not applicable
NDA	new drug application
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
OSIS	Office of Study Integrity and Surveillance

OL	open label
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLWH	people living with HIV
PI	prediction interval
PMR	postmarketing requirement
PO	by mouth, orally
popPK	population pharmacokinetic
PPI	patient package insert
PREA	Pediatric Research Equity Act
PT	preferred term
QD	once daily
OFV	objective function value
rBA	relative bioavailability
RPV	rilpivirine
RRA	Remote Regulatory Assessment
RT	reverse transcriptase
SA	single arm
SAE	serious adverse event
SD	standard deviation
SE	standard error
sNDA	supplemental new drug application
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
USP	United States Pharmacopeia
USPI	United States prescribing information
VF	virologic failure
WHO	World Health Organization
3TC	lamivudine

I. Executive Summary

1. Summary of Regulatory Action

Supplements to NDA 202022 (sNDA S-020 and S-022), containing pharmacokinetic (PK), safety, and efficacy (antiviral activity) Week 48 data from the pediatric clinical study TMC278-TiDP38-C213 (C213), support the Applicant's proposal to expand dosing recommendations for Edurant (rilpivirine [RPV]; 25 mg tablet) in combination with other antiretroviral (ARV) drugs for the treatment of HIV-1 infection in treatment-naïve pediatric patients weighing at least 25 kg and with HIV-1 RNA ≤100,000 copies/mL at the start of therapy. Edurant, in combination with other ARV drugs, resulted in suppression of HIV-1 RNA. The review team recommends the approval of these sNDAs.

NDA 219016 (Original-1), containing PK, safety, and efficacy (antiviral activity) Week 48 data from the pediatric clinical study C213, supports dosing recommendations for Edurant PED, a new rilpivirine (RPV) formulation (2.5 mg tablet for oral suspension), in combination with other ARV drugs for the treatment of HIV-1 infection in treatment-naïve pediatric patients at least 2 years of age and weighing at least 14 kg and with HIV-1 RNA ≤100,000 copies/mL at the start of therapy. Edurant PED, in combination with other ARV drugs, resulted in suppression of HIV-1 RNA. The review team recommends the approval of this NDA. The Applicant concluded that Edurant PED should be recommended for pediatric patients at least 2 years of age and weighing at least 10 kg; however, the review team concluded that this dosing recommendation is only acceptable for pediatric patients at least 2 years of age and weighing at least 14 kg.

Clinical Study TMC278HTX2002 (HTX2002) provided additional PK and safety data to support the dosing recommendations for Edurant and Edurant PED in combination with other ARV drugs for the treatment of HIV-1 infection.

Through the review of NDA 202022 supplements S-020 and S-022 and NDA 219016 (Original-1), no deficiencies that would preclude the approval of these submissions were identified. Similar to other pediatric studies that evaluate safety and efficacy (antiviral activity) of ARVs, Studies C213 and HTX2002 were not powered for inferential statistical analysis of safety or efficacy (antiviral activity). Descriptive statistical methods were used to describe the findings.

The primary basis of the assessment of effectiveness is PK-matching based extrapolation of efficacy. This approach to provides evidence in support of effectiveness of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and adult populations. Based on the review team's assessment, exposures of RPV in pediatric patients living with HIV-1 infection weighing at least 14 kg and receiving the recommended weight-based dosing regimen are comparable to or slightly higher than those observed in treatment-naïve adults living with HIV-1.

The Applicant demonstrated an acceptable safety profile for Edurant and Edurant PED in combination with other antiretroviral drugs for pediatric patients living with HIV-1 infection enrolled in Studies 2C13 and HTX2002. No deaths or serious adverse events were reported, and no adverse events led to study drug discontinuation. Adverse events of special interest (including hypersensitivity reactions/rash, neuropsychiatric, hepatobiliary and potential QT-prolongation-related events) occurred at low rates with the use of RPV, and no new safety signals were identified. The observed risks of RPV use have been described previously, and the rates and nature of the adverse events in Studies 2C13 and HTX2002 were similar to those in adolescents and adults. The Safety Update Report on the use of RPV in pediatric patients was reviewed and no new safety signal was identified.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 4. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HIV-1 infection is a life-threatening and serious disease of major public health significance. • In 2022, there were approximately 39 million people living with HIV worldwide, including an estimated 1.5 million children (range 1.2 to 2.1 million) under 15 years of age.[1] • Globally, approximately 130,000 children acquired HIV in 2022.[1] • There is no vaccine and no post-exposure immunoprophylaxis available for HIV.	• HIV-1 remains a major cause of morbidity and mortality worldwide. If untreated, HIV-1 is a lifethreatening condition, one that affects a large population. HIV-1 infection is a significant public health concern.
Current Treatment Options	• Integrase strand transfer inhibitors (INSTIs) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) have become a preferred regimen for HIV treatment as recommended by the Department of Health and Human Services HIV treatment guidelines for children, adolescents and adults.[2,3]	• While there are approved non-nucleoside reverse transcriptase inhibitor (NNRTI)-, protease inhibitor- and INSTI-based regimens available for the treatment of HIV infection in the pediatric population, there continues to be challenges. For example, poor adherence, and short- and long-term toxicities may contribute to failed therapy and the development of drug resistance. Therefore, it is important to have multiple effective antiretroviral therapies for treatment of HIV infection in the pediatric population. • Long-term viral suppression in children also prevents or leads to fewer complications later in life.

[1] World Health Organization (WHO). HIV Data and Statistics. Available at: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics. Accessed February 27, 2024.
[2] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed February 27, 2024.
[3] Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv. Accessed February 27, 2024.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Benefit	• To support an efficacy claim for the use of Edurant and Edurant PED for the treatment of HIV infection in children at least 2 years of age and weighing and weighing at least 10 kg, the Applicant submitted the 48-week pharmacokinetic, efficacy (antiviral activity), and safety data from two studies (Study C213 and Study HTX2002), which were phase 2, open-label, multicenter, noncomparator studies.
	• In Study C213, 18 treatment-naïve children weighing 17 to 51 kg (age range: 6 to 11 years) with HIV-1 infection, were treated with a weight-based dose of RPV once daily (QD) for 48 weeks.
	  ○ The study demonstrated efficacy among those who received treatment:
	  ▪ 13 participants (13/18; 72%) achieved the efficacy outcome of plasma HIV-1 RNA <50 copies/mL at Week 48.
		• (b) (4)
		• Exposures of RPV with Edurant and Edurant PED were considered acceptable and supported the conclusion that the exposures observed in this weight (age) group are comparable to the exposure observed in adults who received the recommended dose.
		• RPV + two NRTIs provided durable virologic suppression in the treatment-naive pediatric population, and PK-matching based extrapolation supported dosing down to the 14 kg to <20 kg weight band.

Risk and Risk Management	• Participants administered Edurant and Edurant PED in Studies C213 and HTX2002 reported few adverse events (AEs), all of which were considered mild to moderate (Grade 1 or 2 events). • There were no deaths or drug-related serious AEs. • There were no premature discontinuations due to an AE. • No clinically meaningul changes in laboratory values were reportred and most laboratory abnormalities were Grade 1 or 2; Grade 3 laboratory abnormalities included increased amylase, decreased neutrophils and precursors, and decreased estimated glomerular filtration rate. • There were no notable effects of treatment on development or growth (baseline to Week 48) in Tanner stage, height, weight, body mass index, and vital signs. • (6/18, 33%) participants experienced virologic failure on RPV-containing regimens; 5/6 (83%) had treatment-emergent RPV resistance-associated substitutions. In addition, 4/6 (67%) had treatment-emergent resistance substitutions to other drugs in their antiretroviral regimen.	• The frequencies of AEs observed in both studies were generally mild and similar to those noted in adolescents and adults. • A high rate of virologic failure and resistance emergence to RPV and other drugs in the regimen was seen in Study C213 Cohort 2; virologic failure in this population is most likely associated with nonadherence.

2.2. Conclusions Regarding Benefit-Risk

The primary basis of the assessment of RPV effectiveness in pediatric patient populations is PK-matching based extrapolation of efficacy. This is defined as an approach to providing evidence in support of effectiveness of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and adult populations. Studies C213 and HTX2002 did not enroll pediatric participants weighing less than 16 kg and younger than 5.9 years of age. Dosing down to 14 kg is supported based on the available PK data, in addition to PK simulation, and after safety and efficacy considerations for the predicted exposures in children weighing at least 14 kg. The lower body weight limit of 14 kg also aligns with the pediatric weight bands as recommended by the World Health Organization (WHO) for simplified dosing regimens (e.g., 14 kg to less than 20 kg weight band).[4] With respect to age consideration, body weight/size rather than age is the primary determinant for antiretroviral PK exposures in children. Therefore, while no pediatric participant younger than 5.9 years of age was enrolled, it is reasonable to conclude that the recommended dose in children 2 years of age or older weighing at least 14 kg will be safe and effective. Of note, clinical PK and safety data for RPV from pediatric participants at least 2 years of age and weighing at least 10 kg are expected from the ongoing phase 1/2 study, IMPAACT 2036 (CRAYON).[5]

(b) (4)

The safety evaluation for Edurant and Edurant PED was adequate, and the demonstrated clinical safety profile is acceptable for the proposed indication. With all factors considered, the benefits of Edurant and Edurant PED when administered with other ARVs outweigh the risks for the treatment of HIV-1 infection in treatment-naïve pediatric patients at least 2 years of age and weighing at least 14 kg and with HIV-1 RNA ≤100,000 copies/mL at the start of therapy.

[4] World Health Organization (WHO), Drug Optimization. Available at https://www.who.int/tools/aids-free-toolkit/drug-optimization. Accessed March 10, 2024.
[5] IMPAACT 2036. *Study of Oral and Long-Acting Injectable Cabotegravir and Rilpivirine in Virologically Suppressed Children Living With HIV-1, Two to Less Than 12 Years of Age*. NCT05660980; Available at https://clinicaltrials.gov/study/NCT05660980 and https://www.impaactnetwork.org/studies/impaact2036. Accessed February 27, 2024.

II. Interdisciplinary Assessment

3. Introduction

With their supplemental NDAs for Edurant, and original NDA for a new pediatric formulation, Edurant PED, the Applicant is seeking approval for the treatment of HIV-1 infection in treatment-naïve (HIV RNA ≤100,000 copies/mL) and virologically-suppressed pediatric patients at least 2 years of age weighing at least 10 kg. This review highlights the supporting pharmacokinetic (PK), safety, and efficacy (antiviral activity) data in support of the proposed expansion of the pediatric population.

RPV is a NNRTI of HIV-1 and inhibits replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Pharmacodynamic (PD) properties of RPV have been explored previously in adult clinical trials. RPV demonstrated antiviral activity in a 7-day monotherapy trial using RPV at doses ranging from 25 mg to 150 mg, with mean viral load reduction of 1.29 $\log_{10}$ copies/mL with the 25 mg once-daily (QD) dose. Furthermore, RPV, in combination with other ARVs, effectively suppressed HIV-1 RNA replication, as demonstrated during the pivotal phase 3 clinical trials in adults.

The clinical safety experience, pharmacology, and PK profile of RPV have previously been described in adults and adolescents. RPV prolongs the QT interval at doses of 75 mg or higher. At the recommended dose of 25 mg QD, the maximum mean time-matched difference in QTc (correction by Fredericia [QTcF]) interval from placebo was 2.0 milliseconds (ms), which is below the threshold of regulatory concern. At supratherapeutic doses of 75 mg and 300 mg QD, the maximum mean time-matched differences in QTcF interval from placebo was 10.7 and 23.3 ms, respectively. The potential QTc prolongation, hepatic impairment, and drug-drug interaction issues with concomitantly administered drugs metabolized by cytochrome P450 (CYP) enzymes are reflected in the current Edurant label.

The PK/PD exposure-response analyses from phase 2b and 3 trials in adults identified inhibitory quotient (e.g., a ratio between an individual participant's HIV RNA susceptibility [IC_{50}] and RPV C_{trough}) as the key PK parameter that correlated with efficacy outcome. During the phase 2b trial, the 75 mg arm provided higher exposure compared to the RPV 25 mg arm; the efficacy outcome was higher in the RPV 75 mg arm compared to the RPV 25 mg arm. During the phase 3 trial, only the 25 mg dose was evaluated and participants with higher C_{trough} concentrations were less likely to have virologic failure, especially in participants with HIV RNA >100,000 copies/mL.

This application was granted a priority review because the data submitted fulfills a Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR).

3.1. Review Issue List

The review team identified two review issues relevant to the evaluation of benefit (Section II.6.4) and one review issue relevant to the evaluation of risk (Section II.7.6).

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- Are PK modeling and simulation analyses adequate to expand the patient population to <6 years of age or weight <16 kg?
- Are exposures between the adult and pediatric patients receiving the proposed dosing regimen similar to support effectiveness of RPV in pediatric patients?

3.1.2. Key Review Issues Relevant to Evaluation of Risk

- Resistance assessments of virologic failures

3.2. Approach to the Review

Table 5 provides an overview of the clinical studies that substantially contributed to the benefit and risk assessment for RPV.

Table 5. Clinical Studies Submitted in Support of Efficacy and/or Safety Determinations

Study Identifier (NCT#)	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Participants* Actual	No. of Centers and Countries
TMC278-TiDP38-C213 Cohort 2 NCT00799864	ARV treatment-naïve children with HIV-1 infection ≥6 to <12 years of age with a body weight ≥17 kg	Phase 2 Control type: SA Randomization: Non-randomized Blinding: OL	Dosage: Oral RPV • 25 mg PO QD for body weight ≥25 kg • 15 mg PO QD for body weight ≥20 and <25 kg • 12.5 mg PO QD for body weight <20 kg *in combination with two investigator-selected N(t)RTIs*	Primary: PK, safety and tolerability Secondary: Safety, plasma HIV-1 RNA at Weeks 4, 12, 24, and 48, change from baseline in $CD4^+$ cell count and percentage at Week 24 and 48	18	4 sites across 3 countries Republic of South Africa, Thailand, Uganda
TMC278HTX2002 NCT04012931	Virologically-suppressed children with HIV-1 infection ≥2 to <12 years of age with a body weight ≥10 kg	Phase 2 Control type: SA Randomization: Non-randomized Blinding: OL	Dosage: Oral RPV • 25 mg PO QD for body weight ≥25 kg • 15 mg PO QD for body weight ≥20 and <25 kg • 12.5 mg PO QD for body weight <20 kg *in combination with investigator-selected ARVs*	Primary: PK, safety and tolerability Secondary: Safety, PK, proportion with HIV-1 RNA <50, <400, and ≥50, ≥400 copies/mL at Weeks 24 and 48, change in $CD4^+$ cell count and percentage at Week 24 and 48	26	10 sites across 6 countries Italy, Portugal, Republic of South Africa, Spain, Thailand, Uganda

Source: Clinical Reviewer's summary.
* A total of at least 40 participants was planned to be enrolled in Study C213 Cohort 2 and Study HTX2002.
Abbreviations: ARV, antiretroviral; N(t)RTI, nucleoside/nucleotide reverse transcriptase inhibitor; OL, open label; PK, pharmacokinetic(s); PO, by mouth; QD, once daily; RPV, rilpivirine; SA, single arm.

4. Patient Experience Data

Table 6. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The pharmacologic, PK, and clinical pharmacology for RPV were reviewed during original NDA. The key findings from this review are available in the review document as well as Edurant United States Prescribing Information (USPI). No changes or updates are needed based on the review of the current submission.

In this submission, PK data in pediatric patients and information on the relative bioavailability and food effect associated with the new pediatric formulation product have been reviewed. See Section 6.4 for full details.

6. Assessment of Effectiveness

The primary basis of the assessment of effectiveness is PK-matching based extrapolation of efficacy. This is defined as an approach to providing evidence in support of effectiveness of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and adult populations.

6.1. Overview of the Study Designs

6.1.1. Study C213

The completed phase 2 Study C213 was conducted to evaluate the PK, safety, tolerability, and efficacy (antiviral activity) of RPV in combination with other ARVs in treatment-naïve, children and adolescents with HIV-1 who were ≥6 to <18 years of age in two age cohorts: adolescents ≥12 to <18 years of age and weighing ≥32 kg (Cohort 1, results submitted and previously reviewed) and children ≥6 to <12 years of age and weighing ≥17 kg (Cohort 2; results reviewed in this submission). RPV was given in combination with an investigator-selected background regimen consisting of two nucleos(t)ide analogue reverse transcriptase inhibitor (N(t)RTIs; zidovudine [AZT], abacavir [ABC], or tenofovir disoproxil fumarate [TDF] in combination with lamivudine [3TC] or emtricitabine [FTC], whichever were approved and marketed or considered local standard of care for children ≥6 to <12 years of age in a particular country). The background regimen was given as the co-formulation or as the separate components according to local availability and use in the country. Cohort 2 was conducted at multiple sites in the Republic of South Africa, Thailand, and Uganda.

All newly recruited participants started treatment until they reached a total treatment duration of 48 weeks or at early discontinuation. When participants increased in weight such that they changed weight categories, their dose was adjusted as per the dose recommendations. The final analysis (including the 48-Week initial treatment and post-Week 48 extension periods) was performed when all Cohort 2 participants had reached at least 48 weeks of treatment, rolled over to Study TMC278IFD3004 (IFD3004), or discontinued earlier.

Disposition

In Cohort 2, a total of 18 participants were enrolled and received either RPV 25 mg PO QD (body weight of ≥25 kg, or <25 kg if enrolled prior to Protocol Amendment 10), RPV 15 mg PO QD (body weight of ≥20 to <25 kg) or RPV 12.5 mg PO QD (body weight of <20 kg) in combination with an investigator-selected background regimen of two N(t)RTIs (see Table 7). Participants who were enrolled before Amendment 10 received 25 mg PO QD regardless of body weight. All participants who received the 25 mg dose took the single 25 mg tablet formulation.

Table 7. Participants Enrolled and Treated, Full Analysis Set, Study C213 Cohort 2

	12.5 mg PO QD, <20 kg	15 mg PO QD, 20 to <25 kg	25 mg PO QD, <25 kg	25 mg PO QD, ≥25 kg	All RPV Recommend Dose*	All Participants
Number of participants treated with RPV (FAS)	2 (11%)	2 (11%)	5 (28%)	9 (50%)	13 (72%)	18 (100%)

Source: Clinical Reviewer's analysis (JMP v. 16.2.0) of the adsl.xpt dataset.
* RPV Recommended dose: 12.5 mg PO QD for <20 kg, 15 mg PO QD for 20 to <25 kg, 25 mg PO QD for ≥25 kg.
Abbreviations: FAS, full analysis set; PO, by mouth; RPV, rilpivirine; QD, once daily.

Of the 18 participants, 17 (94%) participants completed the 48-week treatment period, and 12 (67%) participants entered the post-Week 48 treatment extension period. Two participants changed RPV dose because of weight increases, from 15 mg PO QD to 25 mg PO QD; for one of these participants this happened at time of roll-over into study IFD3004. The median duration of exposure for participants in the Week 48 analysis (including post-Week 48 extension) was 69.5 weeks (range: 34.9 to 218.3 weeks).

Demographics and Baseline Characteristics

The full analysis set (FAS) included 18 participants. The majority of the participants were male (61%) and Black (89%). The median age was 9.0 years (range: 6 to 11 years), and the median weight was 25.0 kg (range: 17.0 to 51.4 kg). A summary of baseline characteristics stratified by study is located in Section III.12.2.1 (Table 21).

Most participants (17 of 18; 94%) acquired HIV-1 via mother-to-child transmission (MTCT). The median duration of known HIV-1 infection was 0.1 years (range 0 to 6.2 years). The median baseline HIV-1 RNA was 55,400 copies/mL (range: 567 to 149,000 copies/mL). Four of the 18 (22%) participants had a baseline HIV-1 RNA of >100,000 copies/mL but were eligible to enter the study since they had ≤100,000 copies/mL at screening. The median absolute baseline $CD4^+$ cell count was 433 cells/mm^3 (range: 12 to 2068 cells/mm^3). At baseline, all 18 participants were receiving 3TC, with either ABC (56%), AZT (33%), or TDF (11%). Seven out of 18 participants (all in the 25 mg; <25 kg and ≥25 kg dose-weight groups) were infected with HIV-1 subtype C. In the low dose-weight groups (<20 kg and ≥20 to<25 kg) subtypes A, A/D, and A1 were observed. From the seven female participants, six participants had Tanner Stage I and one participant had Tanner Stage II for pubic hair at baseline, and five participants had Tanner Stage I and two participants had Tanner Stage II for genitalia/breasts at baseline. All 11 male participants had Tanner Stage I for genitalia and pubic hair at baseline.

6.1.2. Study HTX2002

Study HTX2002 was conducted to evaluate the PK, safety, tolerability, and efficacy (antiviral activity) of RPV in combination with other ARVs in virologically-suppressed (HIV-1 RNA <50 copies/mL) children with HIV-1 infection who were ≥2 to <12 years of age and weighing ≥10 kg and without a history of virologic failure or documented resistance to RPV. Dose adjustments of RPV due to changes in body weight, if applicable, were allowed.

The participants continued RPV and ARV background regimen and the final analysis was performed when all participants reached Week 48 or discontinued earlier. Study HTX2002 was conducted at multiple sites in Italy, South Africa, Spain, Thailand, Portugal, and Uganda.

Disposition

A total of 26 participants were enrolled and treated with RPV (12.5 mg, 15 mg, or 25 mg PO QD) in combination with the investigator-selected background ARVs. Of the 26 participants enrolled, 1 (4%) participant was 2 to <6 years of age and 25 (96%) participants were 6 to <12 years of age. All participants completed the Week 24 visit, and 23 (89%) participants completed the Week 48 visit. Table 8 presents data by dose-weight group, which was based on the initial dose each participant started with, irrespective of changes in weight-based dosing recommendation or subsequent individual dose modifications (due to individual weight alterations during the study). All participants who received the 25 mg dose took the single 25 mg tablet formulation. All 26 participants who were enrolled received at least one dose of RPV and were included in the FAS.

Table 8. Participants Enrolled and Treated, Full Analysis Set, Study HTX2002

	12.5 mg PO QD, <20 kg	15 mg PO QD, <20 kg	15 mg PO QD, 20 to <25 kg	25 mg PO QD, ≥25 kg	All RPV Recommend Dose*	All Participants
Number of participants treated with RPV (FAS)	1 (4%)	2 (8%)	5 (19%)	18 (69%)	24 (92%)	26 (100%)

Source: Clinical Reviewer's analysis (JMP v. 16.2.0) of the adsl.xpt dataset.
Abbreviations: PO, by mouth; RPV, rilpivirine; QD, once daily.
* RPV Recommended dose: 12.5 mg PO QD for <20 kg, 15 mg PO QD for 20 to <25 kg, 25 mg PO QD for ≥25 kg.

Three participants had dose adjustments because of weight increases during the study: two participants switched from 15 mg PO QD to 25 mg PO QD and one participant changed from 12.5 mg PO QD to 15 mg PO QD. One participant who had taken the wrong (higher) 15 mg dose was switched to 12.5 mg after 4 weeks. The median duration of exposure for participants in the Week 48 analysis was 48.4 weeks (range: 47.0 to 52.3 weeks).

Demographics and Baseline Characteristics

The FAS included 26 participants. The majority of the participants were male (62%) and Black (50%). The median age was 9.9 years (range: 5.9 to 11.9 years), and the median weight was 28.1 kg (range: 16.2 to 60.0 kg). One (4%) participant was 2 to <6 years, 8 (31%) were 6 to <9 years, and 17 participants (65%) were 9 to <12 years of age. Three (12%) participants weighed <20 kg, 5 (19%) participants weighed 20 to <25 kg, and 18 (69%) participants weighed ≥25 kg. A summary of baseline characteristics, stratified by study is located in Section III.12.2.1, Table 21.

Most participants (24 of 26; 92%) acquired HIV via MTCT. The median duration of known HIV-1 infection was 7.6 years (range 0.9 to 11.6 years). The median baseline HIV-1 RNA was 1 copy/mL (range: 1 to 125 copies/mL). Twenty-five (96%) participants had a baseline plasma HIV-1 RNA of <50 copies/mL, and 1 (4%) participant had a baseline plasma HIV-1 RNA of ≥50 copies/mL (but was eligible to enter the study since viral load was <50 copies/mL at screening). The median absolute baseline $CD4^+$ cell count was 882 cells/mm^3 (range: 458 to 1,327 cells/mm^3). At baseline, 20 (77%) participants were receiving 3TC with ABC. The most prevalent HIV-1 subtypes in the 6 to <12 years age group were subtype C (5 [26%] participants) and subtype AE (4 [21%] participants). The participant in the 2 to <6 years age group was infected with HIV-1 subtype A.

For female participants in the 6 to <12 years age group, the Tanner stage for pubic hair was I for 5 (56%) participants and II for 4 (44%) participants. For breasts, the Tanner stage was I, II, and III for 4 (44%), 3 (33%), and 2 (22%) female participants, respectively. Most male participants had Tanner stage I for both pubic hair (13 [81%) participants) and genitalia (12 [75%) participants).

6.1.3. Overall Extent of Exposure

At total of 44 participants were enrolled in Studies C213 Cohort 2 and HTX2002. Enrollment by the different age and weight groups is presented in Table 9. All participants enrolled also received at least one dose of RPV and were therefore included in the FAS. The FAS was used as the primary and only population for all endpoint analyses.

Table 9. Enrollment by Age and Weight Group at Baseline Across Studies C213 and HTX2002

	Study C213 Cohort 2	HTX2002	Combined
Total Number of Participants Enrolled	18	26	44
Age (categorical), n (%)			
2 to <6 years	Not enrolled	1 (4)	1 (2)
6 to <9 years	8 (44)	8 (31)	16 (36)
9 to <12 years	10 (56)	17 (65)	27 (61)
Weight (categorical) at baseline, n (%)			
<20 kg	2 (11)	3 (12)	5 (11)
20 to <25 kg	7 (39)	5 (19)	12 (27)
≥25 kg	9 (50)	18 (69)	27 (61)

Source: Clinical Reviewer's analysis (JMP v.16.2.0) of the adsl.xpt datasets

6.1.4. RPV Formulations and Doses Administered and Evaluated in Study C213 and Study HTX2002

Two different formulations of RPV were used in Studies C213 and HTX2002.

- For the 25 mg dose, a commercially available oral RPV tablet was formulated as an oral filmcoated tablet, containing 27.5 mg of RPV as the hydrochloric acid salt, equivalent to 25 mg of RPV (1 × 25 mg tablets) as the free base. The 25 mg RPV tablet was to be swallowed whole and could not be chewed, broken, or crushed.

- For the 15 mg (6 × 2.5 mg tablets) and 12.5 mg (5 × 2.5 mg tablets) weight-adjusted dosing, RPV was formulated as an investigational tablet containing 2.75 mg of RPV as the hydrochloric acid salt, equivalent to 2.5 mg of RPV as the free base. The tablets had to be dispersed prior to use.

Per protocol dosing recommendations could be altered based on accumulating data; specifically, dose modifications occurred two times during the conduct of these studies. Initially, all participants, regardless of body weight, were planned to receive RPV 25 mg PO QD. The analysis of the first 10 participants in Cohort 2, including PK modeling and simulation to further assess the RPV pediatric dose based on accumulating data, was discussed with the IDMC. Based on the data, the IDMC agreed with the proposed doses of RPV the protocol amendment 10 of Study C213 and protocol amendment 2 of Study HTX2002:

- RPV 25 mg PO QD with food for participants with a body weight ≥25 kg
- RPV 15 mg PO QD (6×2.5 mg tablets) with food for participants with a body weight <25 kg.

An additional analysis of the available PK data and all available safety, tolerability, and antiviral activity/efficacy data from both Study C213 Cohort 2 and Study HTX2002 were reviewed by the Sponsor and the IDMC to assess appropriateness of the dose. Based on the data, the following RPV dose recommendations were applied to any new participant recruited in the ongoing pediatric studies:

- RPV 25 mg PO QD with food for participants with a body weight of ≥25 kg
- RPV 15 mg PO QD (6×2.5 mg tablets) with food for participants with a body weight of ≥20 to <25 kg
- RPV 12.5 mg PO QD (5×2.5 mg tablets) with food for participants with a body weight of <20 kg

6.2. Results from Study C213 Cohort 2

All 18 participants that were enrolled (All Enrolled Analysis Set), received at least one dose of RPV and were included in the FAS. Of the 18 participants, 17 (94%) participants completed the 48-week treatment period; 1 (6%) participant discontinued the study early during the 48-week treatment period due to reaching a virologic endpoint.

Based on the FDA Snapshot algorithm, virologic response (defined as HIV-1 RNA <50 copies/mL) at Week 48 was achieved in 13 of 18 (72%) participants, while virologic failure was observed in 3 of 18 (17%) participants, as summarized in Table 11. Two of 18 (11%) participants in the 15 mg PO QD (20 to ≤25 kg) dose group had missing HIV-1 RNA data at Week 48 but remained on study; the latest available HIV-1 RNA for these 2 participants was <50 copies/mL post-Week 48 and prior to Week 48, respectively.

Table 10. Virologic Outcomes for Week 48 (Snapshot Analysis), Full Analysis Set, Study C213 Cohort 2

Virologic Outcome Week 48	N=18 n (%)
HIV-1 RNA <50 copies/mL	**13 (72)**
HIV-1 RNA ≥50 copies/mL	**3 (17)**
Data in window not below threshold HIV-1 RNA ≥50 copies/mL in Week 48 Window	2 (11)
Discontinue Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥50 copies/mL	1 (6)
No Virologic Data	**2 (11)**
On study but missing data in window	2 (11)

Source: Clinical Reviewer's analysis (JMP v.16.2.0) of the advl.xpt dataset and Applicant's Summary of Clinical Study Final Report (Table 10, p. 54).
* Other reason specified as reaching a virologic endpoint.

Baseline HIV-1 RNA has been previously identified to have influence on response (and maintenance of response) to RPV. In adult trials (TMC278-C209 and TMC278-C215), participants with baseline HIV-1 RNA >100,000 had higher rate of virologic failure compared to those with lower baseline HIV-1 RNA. The proportion of adult participants with HIV-1 RNA <50 copies/mL at Week 48 was 83% for the overall population and 89% among participants with baseline HIV-1 RNA ≤100,000 copies/mL. The following subgroup analyses were also performed for Study C213 Cohort 2. The response rate was similar (71%) after the exclusion of the four participants with baseline HIV-1 RNA >100,000 copies/mL, as summarized in Table 11.

Table 11. Virologic Outcome for Week 48 (Snapshot Analysis) by Baseline HIV-1 RNA ≤100,000 copies/mL, Study C213 Cohort 2

Virologic Outcome Week 48	N=14 n (%)
HIV RNA <50 copies/mL	**10 (71)**
HIV RNA ≥50 copies/mL	**2 (14)**
Data in window not below threshold HIV-1 RNA ≥50 copies/mL in Week 48 Window	1 (7)
Discontinue Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥50 copies/mL	1 (7)
No Virologic Data	**2 (14)**
On study but missing data in window	2 (14)

Source: Clinical Reviewer's analysis (JMP v. 16.2.0) of the advl.xpt dataset
* Other reason specified as reaching a virologic endpoint.

The observed success trend in this pediatric population is generally comparable to that observed during the adult trials. Although the efficacy outcome in pediatric participants was lower than treatment-naïve adult participants at Week 48, the difference was not related to the RPV exposures, because the exposures of RPV in pediatric trial participants receiving the recommended weight-based dosing regimen were comparable or slightly higher than those obtained in treatment-naïve adults with HIV-1 infection. The outcome disparity may be related to smaller sample size and/or decreased adherence.

The majority of participants (14 of 18 [78%]) had an adherence to RPV treatment >95% through Week 48. Four of 18 (22%) participants had an adherence to RPV treatment ≤95% during the 48-week treatment period: one participant in the 25 mg (≥25 kg) group, two participants in the 25

mg (<25 kg) group (one of whom had adherence >65% to ≤80%), and one participant in the 12.5 mg (<20 kg) group. From these four participants with adherence ≤95%, three participants showed virologic response (HIV-1 RNA <50 copies/mL) at Week 48 (although HIV-1 RNA >50 copies/mL was reported as of Week 60, Week 72, and Week 120 in one participant) and one participant was a virologic failure at Week 48. See Section 7.6.1 for additional details.

The mean change (standard error [SE]) in $CD4^+$ cell count from baseline was 163.9 (49.2) cells/μL and 215.9 (62.4) cells/μL at Weeks 24 and 48, respectively. At Week 24, the mean change from baseline (SE) was 146.5 (21.5), 167.3 (38.6), and 165.3 (87.8) cells/μL in participants with a $CD4^+$ cell count of <200 cells/μL, 200 to ≤400 cells/μL, and >400 cells/μL, respectively. At Week 48, the mean change from baseline (SE) was 128.0 (128.0), 195.0 (42.4), and 246.0 (109.5) cells/μL in participants with a $CD4^+$ cell count of <200 cells/μL, 200 to ≤400 cells/μL, and >400 cells/μL, respectively. The mean change from baseline (SE) in CD4% was 6.6 (0.9) at Week 24 and 8.2 (1.4) at Week 48.

6.3. Results from Study HTX2002

Efficacy (antiviral activity) was assessed based on virologic outcome (proportion of participants with HIV-1 RNA <50 copies/mL) and virologic failure using the FDA Snapshot algorithm at Week 24 (primary analysis) and Week 48 (final analysis). All 26 participants who were enrolled received at least one dose of RPV and were included in the FAS. Efficacy was analyzed using descriptive statistics on the FAS.

At Week 24 and Week 48, 100% of participants remained virologically suppressed (HIV-1 RNA <50 copies/mL) and none had virologic failure. The mean (SE) change in $CD4^+$ cell count from baseline was 37.3 (32.8) cells/mm^3 and –8.4 (29.7) cells/mm^3 at Week 24 and Week 48, respectively. Because this analysis of $CD4^+$ cell counts included a small number of virologically-suppressed participants, slight variability was expected.

6.4. Key Review Issues Relevant to Evaluation of Benefit

6.4.1. Are PK modeling and simulation analyses adequate to expand the patient population to <6 years of age or weight <16 kg?

Issue

A limited number of pediatric participants in younger age groups and weight bands were enrolled in Studies C213 and HTX2002.

Background

The course of the disease and the expected response to RPV is expected to be sufficiently similar in the pediatric and adult populations.

Assessment

Sparse PK samples in all pediatric participants and intensive PK samples in subset of pediatric participants were collected in Studies C213 and HTX2002 (see Section 6.1 for study design, number of participants, and the distribution of age and body weight).

Table 12. Population Pharmacokinetic Estimates of Rilpivirine After Administration of the Recommended Daily Oral Dosing Regimen in Pediatric Patients ≥6 to <18 years (Study C213)[a]

Pharmacokinetics of RPV[b] Mean±SD Median (range)	**12.5 mg once daily** <20 kg	**15 mg once daily** ≥20 to <25 kg	**25 mg once daily** ≥25 kg
N	2	2	44
AUC_{24h} (ng.h/mL)	1974, 2707 NA (1974 – 2707)	1912, 2477 NA (1912 – 2477)	2536±979 2413 (973 – 4848)
C_{0h} (ng/mL)	68.1, 86.7 NA (68.1 – 86.7)	48.3, 80.0 NA (48.3 – 80.0)	87.0±34.5 82.7 (27.8 – 171)

[a] The 12.5 mg and 15 mg doses were administered as 5 and 6 dispersed 2.5 mg tablets, respectively. The 25 mg dose was administered as one 25 mg tablet. Mean rilpivirine exposure was approximately 40% higher in TMC278HTX2002 compared to TMC278-C213

[b] Individual data when N=2

RPV= rilpivirine; NA = not applicable; SD = standard deviation

Table 13. Population Pharmacokinetic Estimates of Rilpivirine After Administration of the Recommended Daily Oral Dosing Regimen in Pediatric Patients ≥2 to <18 years (Study TMC278HTX2002)[a]

Pharmacokinetics of RPV[b] Mean±SD Median (range)	**12.5 mg once daily** ≥10 to <20 kg	**15 mg once daily** ≥20 to <25 kg	**25 mg once daily** ≥25 kg
N	2	5	18
AUC_{24h} (ng.h/mL)	4375, 5057 NA (4375 – 5057)	3541±949 3112 (2689 – 4947)	4195±1056 4016 (2732 – 6260)
C_{0h} (ng/mL)	151, 163 NA (151 – 163)	112±39.8 91.8 (73.7 – 172)	134±38.7 121 (78.9 – 220)

[a] The 12.5 mg and 15 mg doses were administered as 5 and 6 dispersed 2.5 mg tablets, respectively. The 25 mg dose was administered as one 25 mg tablet. Mean rilpivirine exposure was approximately 40% higher in TMC278HTX2002 compared to TMC278-C213

[b] Individual data when N=2

RPV= rilpivirine; NA = not applicable; SD = standard deviation

The pediatric studies did not enroll participants with a body weight lower than 16 kg and younger than 5.9 years old. Despite this lack of data, the Applicant proposed the use of RPV in pediatric patients weighing at least 10 kg and older than 2 years old. To support the proposed dosing regimen, the Applicant conducted PK simulations to predict the effect of body weight on RPV exposure metrics (AUC_{ss} and $C_{max,ss}$) and compare RPV exposure metrics between pediatric patients (with a body weight down to 10 kg) and adults.

According to the Applicant, the predicted distribution of AUC_{ss} appears to be higher than the predicted exposure in adults (Studies C209 and C215), particularly for the weight bands of 10 to 16 kg and 25 to 40 kg. The predicted 90% prediction interval (PI) of $C_{max,ss}$ was below the safety threshold for QTc prolongation, as determined by the Applicant, of 750 ng/mL across the entire body weight range at the proposed doses (see Section III.12.2.2, Figure 8).

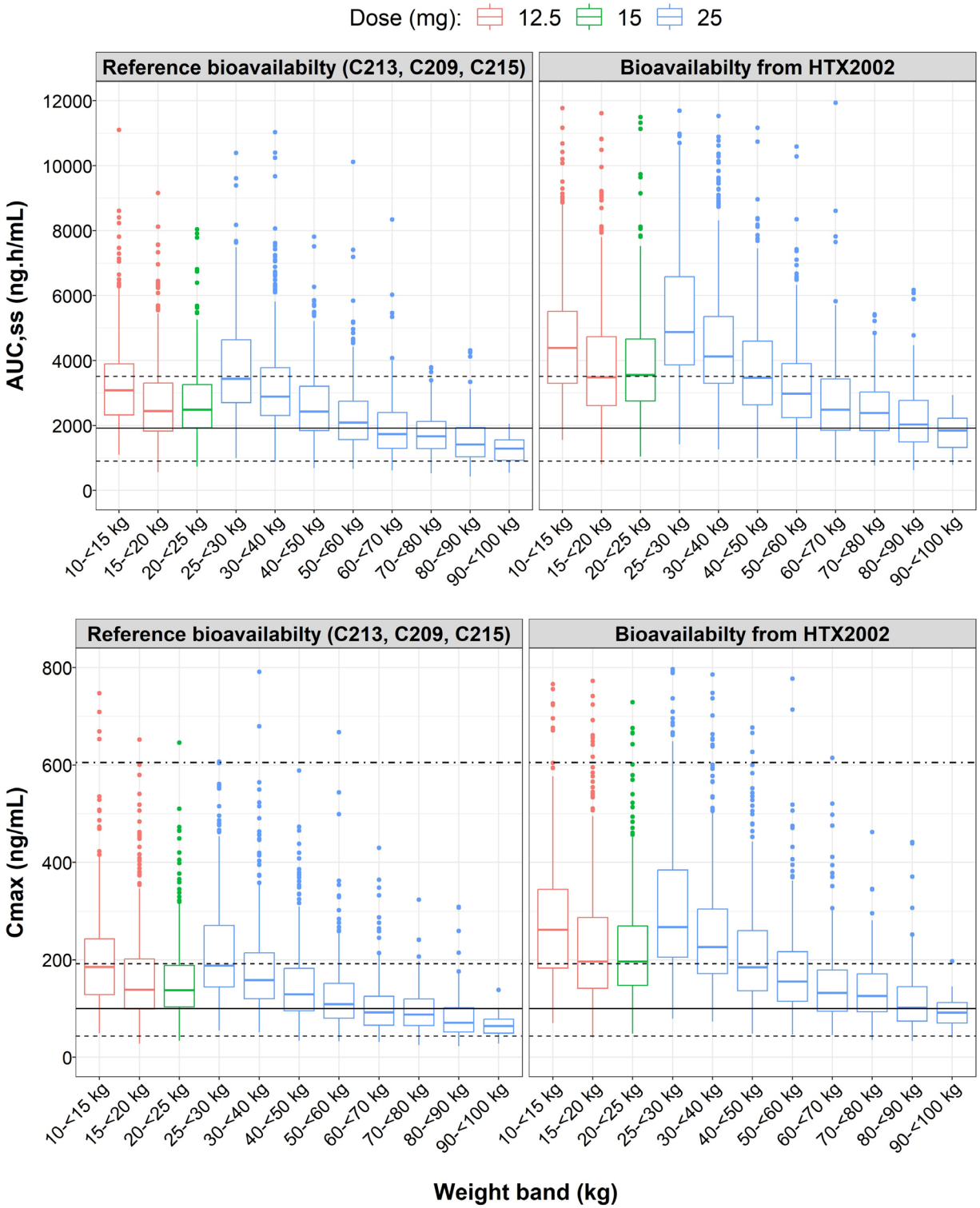
Of note, higher exposures of RPV were observed in Study HTX2002 compared to Study C213 for unknown reasons. The contributing factor(s) for the higher exposure have not been elicited. For population pharmacokinetic (popPK) modeling and simulation, this difference was handled as a study-specific high bioavailability (i.e., 43% higher bioavailability with HTX2002). Therefore, the predicted higher AUC_{ss} in pediatrics compared to adults from the Applicant's PK simulations is likely driven by setting a 43% higher bioavailability in half of the simulated population, although the higher bioavailability was observed only in HTX2002.

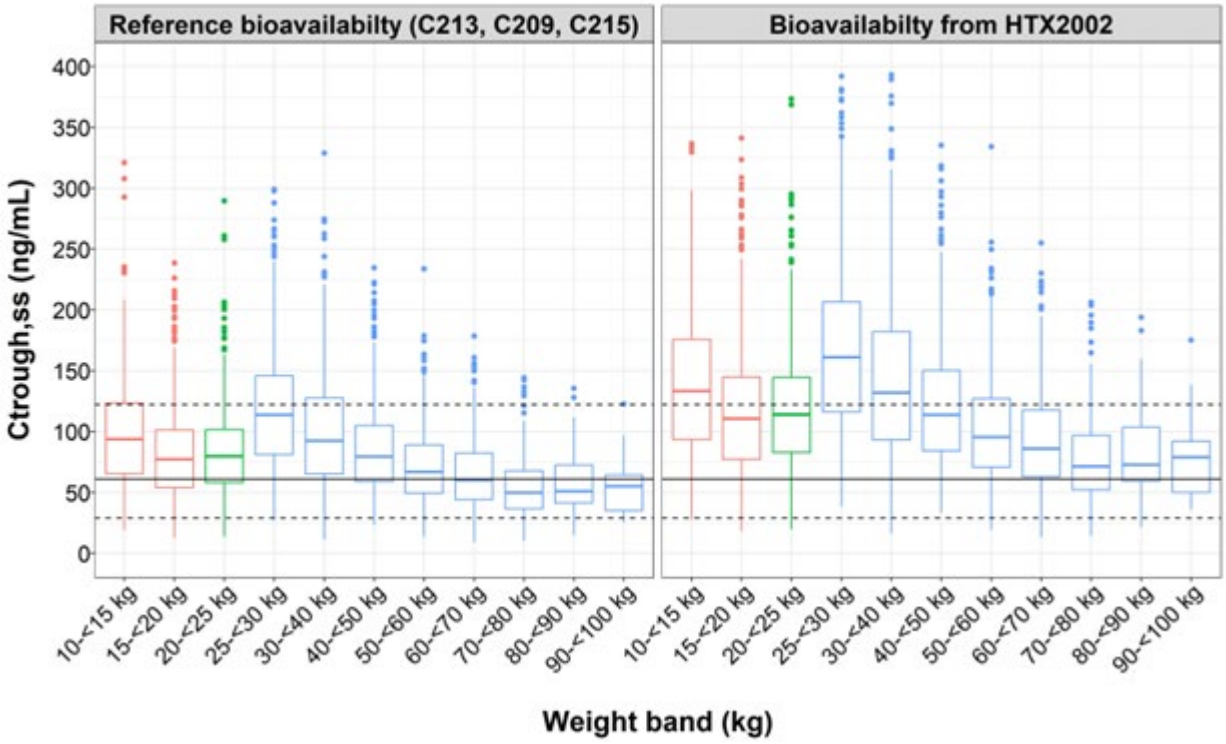
To address this issue, the reviewer conducted independent PK simulations to assess two different scenarios:

- PK simulations were performed with the reference bioavailability and typical apparent PK parameters estimated from pediatric study C213 (cohort 1 and cohort 2) and adult studies (C209 and C215).
- PK simulations were conducted with a 43% higher bioavailability, as estimated for HTX2002.

Based on both PK simulation scenarios, the proposed dosing regimen appears to be acceptable and safe regarding the potential for QTc prolongation (See Section III.12.2.2, Figure 10 and Figure 11). However, it's important to note that Study C213 Cohort 2 and Study HTX2002 did not enroll pediatric patients with a body weight less than 16 kg, resulting in a lack of observed PK and safety information for participants weighing between 10 and 15 kg. Therefore, the proposed dosing regimen was limited to participants down to 14 kg, as this cutoff was more proximal to the lowest body weight observed in these two pediatric studies. Additionally, practical considerations were taken into account in determining the lowest weight band; per WHO's simplified dosing regimens for children living with HIV, 14 kg is the lower limit for one of the weight bands (i.e., 14 to less than 20 kg). Additionally, despite the absence of data in pediatric patients less than 5.9 years old, the extension of the proposed dosing regimen to pediatric patients aged 2 years and older is supported because body weight/size rather than age is the primary determinant for PK. Therefore, basing the dosing regimen on body weight ensures appropriate exposures in pediatric patients within this age range.

Figure 1. Predicted RPV AUC_{ss} and C_{max} by Weight Group, Stratified by Estimated Bioavailability





Note: The solid and dotted lines are the overall median and 90% prediction interval predicted from studies in adults (C209 and C215, range of weight= 43 to 102 kg). The dot-dashed line at the Cmax of 605 ng/mL is the concentration associated with 10 milliseconds increase in QTC in previous TQT studies.
Source: FDA reviewer.

Conclusion

The currently available efficacy and PK data from controlled trials of RPV in adults and the PK data from Studies C213 and HTX2002 support the extrapolation of efficacy from adults to treatment-naïve pediatric patients aged at least 2 years and weighing at least 14 kg. PopPK analysis indicated that the exposures of RPV in pediatric patients with HIV-1 infection weighing at least 14 kg and receiving the recommended weight-based dosing regimen are comparable or slightly higher than those observed in treatment-naïve adult patients with HIV-1 infection.

6.4.2. Do available data support the use of proposed pediatric formulation?

Issue

The Applicant has proposed the use of a new age-appropriate oral tablet formulation suitable for pediatric use.

Background

A relative bioavailability (rBA) and food effect study (Study TMC278IFD1008) was conducted to support the use of the new proposed dispersible tablets.

Assessment

Study TMC278IFD1008 was conducted to determine the rBA of RPV following the administration of a single dose of two different oral dispersible tablet formulation candidates and of an oral granule formulation, compared to the administration of a single dose of the 25 mg marketed oral tablet under fed conditions in healthy adult participants. As shown in

Table 14, the geometric mean values of RPV AUC and C_{max} were 33% and 28% higher, respectively, for the proposed 10 × 2.5 mg tablets for oral suspension (Treatment C) as compared to 1 × 25 mg marketed tablet (Treatment A).

Table 14. Summary of the Statistical Analysis of the Pharmacokinetic Parameters of RPV After Single Dose Administration of Oral RPV 25 mg Formulated as Dispersible Tablets (G009-01) and as a Single Tablet (Edurant), Following a Standardized Breakfast (Panel 1) (Study TMC278IFD1008)

Parameter	LSmeans		LSmeans ratio	90% CI
	Treatment A 1 Tablet of RPV (EDURANT) (reference)	Treatment C 10 Dispersible Tablets of RPV (G009-01) (test 2)		
n	16	15		
C_{max}, ng/mL	92.6	118	127.61	(114.16 – 142.64)
AUC_{last}, ng.h/mL	3397	4124	121.40	(110.16 – 133.78)
AUC_{∞}, ng.h/mL[a]	3315	4397	132.64	(115.09 – 152.86)

[a] n=9 for reference and n=11 for test; Source: Table 7 of the Applicant's TMC278IFD1008 study report

As shown in Table 15, the AUC_{∞} of RPV administered as the 2.5 mg tablets for oral suspension under fasted conditions was 31% lower compared to the AUC_{∞} under fed conditions. When administered with yogurt only, the AUC_{∞} was 28% lower than when taken with a standard breakfast. Dispersion of the 2.5 mg tablets in an acidic fluid (orange juice) compared with dispersion in water increased the AUC_{∞} by 12%. Similar results were observed for C_{max} and AUC_{last}. The effect of food on the bioavailability of RPV is generally consistent when administered as the 2.5 mg tablets for oral suspension or as the marketed 25 mg tablet. Similar to the market formulation, the RPV 2.5 mg tablets should be taken with a meal.

Table 15. Statistical Analysis of the PK Parameters of RPV After Single-dose Administration of 25 mg RPV as 10 × 2.5 mg Dispersible Tablet Formulation G009-01 Under Differing Food and Dispersion Liquid Conditions (Study TMC278IFD1008); as Compared to the Effect of Food on RPV PK for the Marketed Formulation (Study TMC278-TiDP6-C137)

Parameter	Treatment	N	LS Mean	LS Mean Ratio (%)	90% CI (%)
C_{max} (ng/mL)	*Reference:* dispersed in water; standard breakfast	16	121	-	-
	Dispersed in water; fasted	16	79.8	65.79	56.40-76.75
	Dispersed in orange juice; standard breakfast	16	135	111.45	95.54-130.01
	Dispersed in water; yogurt	16	100	82.49	70.71-96.23
	Reference: dispersed in water; fasted	16	79.8	-	-
	Dispersed in water; yogurt	16	100	125.39	107.49-146.28
AUC_{last} (ng*h/mL)	*Reference:* dispersed in water; standard breakfast	16	4171	-	-
	Dispersed in water; fasted	16	2990	71.68	62.84-81.76
	Dispersed in orange juice; standard breakfast	16	4751	113.90	99.86-129.92
	Dispersed in water; yogurt	16	3001	71.95	63.08-82.07
	Reference: dispersed in water; fasted	16	2990	-	-
	Dispersed in water; yogurt	16	3001	100.38	88.01-114.50
AUC_{∞} (ng*h/mL)	*Reference:* dispersed in water; standard breakfast	11	4697	-	-
	Dispersed in water; fasted	11	3223	68.62	56.75-82.97
	Dispersed in orange juice; standard breakfast	12	5281	112.42	93.70-134.89
	Dispersed in water; yogurt	13	3380	71.96	60.09-86.17
	Reference: dispersed in water; fasted	11	3223	-	-
	Dispersed in water; yogurt	13	3380	104.87	87.95-125.05
Study TMC278-TiDP6-C137; 75 mg single dose administered as 75 mg Phase 3 tablet					
C_{max} (ng/mL)	*Reference:* standard breakfast	19	275.8	-	-
	Fasted	19	150.2	54.45	42.92-69.07
AUC_{last} (ng*h/mL)	*Reference:* standard breakfast	19	9683	-	-
	Fasted	19	5546	57.27	45.72-71.75
AUC_{∞} (ng*h/mL)	*Reference:* standard breakfast	19	10620	-	-
	Fasted	19	6269	59.02	46.87-74.32

Source: Tables 3 and 4 of the Applicant's Summary of Biopharmaceutics.

Conclusion

The results from the relative bioavailability (rBA) and food effect study (Study TMC278IFD1008) support the use of the proposed pediatric formulation (RPV 2.5 mg tablets for oral suspension) in pediatric patients 2 years of age and older, weighing at least 14 kg and less than 25 kg. However, it cannot be used as a substitution for the current marked RPV 25 mg tablets on a milligram-per-milligram basis due to the difference in relative bioavailability. In addition, RPV 2.5 mg tablets should be taken with a meal, as required for RPV 25 mg tablets.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The preclinical evaluation of RPV included over 55 trials to assess the safety pharmacology, PK, general toxicology, carcinogenicity, reproductive and developmental toxicology, genetic

toxicology and local tolerance in mice, rats, rabbits, dogs and cynomolgus monkeys. Please refer to the original review of NDA 202022 for full details.

One of the primary toxicity findings in nonclinical studies were adrenal effects, generally characterized by increased serum progesterone and decreased cortisol levels, observed in rats, dogs, cynomolgus monkeys, and possibly mice. These effects are thought to be associated with an inhibition of steroidogenesis at the level of CYP450 21-hydroxylase (CYP21) and 17-hydroxylase (CYP17; inhibition of the latter was observed in cynomolgus monkeys only). In dogs, findings of premature activation and overstimulation of the ovaries may also be related to inhibition of steroidogenesis. Those effects on dog ovaries were noted at exposures 8 to 25 times higher than clinical exposures at the recommended dose of 25 mg once daily. Premature ovulation, as was noted in immature dogs treated for four weeks, was not seen in immature cynomolgus monkeys treated for 8 weeks, although the lack of an early puberty effect in the monkeys may be related to the young age of the monkeys and the fact that the monkeys were still pre-pubertal at the end of the study.

Of note, extensive adrenal monitoring was included during the adult and adolescent clinical trials. Adrenal function monitoring plans (e.g., adrenocorticotropic hormone [ACTH] stimulation testing) were also included for the pediatric studies, as further discussed in the clinical safety section.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

7.2.1. QT prolongation

In healthy adult participants, RPV 75 mg QD and 300 mg QD (3 times and 12 times the dose in Edurant) were shown to prolong the QTc interval of the electrocardiogram (ECG). Refer to the current USPI and original NDA review of Edurant for full details.

In addition to the assessment of individual potential QT-prolongation-related events (see Sections II.7.5.1.5 and 7.5.3.1.1), the exposure-QTcF relationship for time-matched plasma concentration and delta-QTcF was graphically explored for pediatric patients in Studies C213 and HTX2002. No trend was identified for time-matched RPV observed concentrations and delta QTcF (see Section III.12.2.3). The analysis indicates that the proposed dosing regimen is not anticipated to pose new or additional QT-prolongation safety concerns in pediatric patients as compared to adults.

7.3. FDA Approach to the Safety Review

The review team did not identify any major data quality or integrity issues that preclude performing a safety review. No major issues were identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for the events reported in Studies C213 and HTX2002 were coded according to Version 25.0 and 25.1, respectively; the translations were reviewed and were found to be acceptable.

7.3.1. Sources of Data for Clinical Safety Assessment

The data submitted support safety and tolerability of Edurant and Edurant PED when administered in combination with other ARVs in children at least 2 years of age and weighing at least 14 kg. The types of AEs observed were similar to adults and adolescents, and no new safety concerns were identified.

Data from the following two phase 2 studies formed the basis of the clinical safety evaluation:

- Study 2C13: Final analysis of Cohort 2, including the 48-week initial treatment and post-Week 48 extension periods that evaluated oral RPV in combination with an investigator-selected background regimen containing two N(t)RTIs in ARV treatment-naïve children with HIV-1 infection, ≥6 to <12 years of age and weighing ≥17 kg.
- Study HTX2002: Final analysis at Week 48 that evaluated oral RPV in combination with other ARVs in virologically-suppressed children with HIV-1-infection, ≥2 to <12 years of age and weighing ≥10 kg.

The Applicant submitted safety data from a total of 44 pediatric participants who enrolled in Studies C213 Cohort 2 and HTX2002 and received at least one dose of RPV. The studies were not powered or designed to have an active comparator arm, nor was there a pre-specified number of participants required for testing statistical differences in AE incidences. Descriptive statistics were therefore applied to describe the observed findings.

7.3.2. Safety Analysis Plan and Definitions

The prespecified safety analysis plan and definitions were reviewed during the protocol development and were acceptable to the clinical review team. Use of descriptive statistics was predefined in the protocol for summarizing the safety outcomes. The review team agreed with the proposed approach.

The protocols specified use of the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events toxicity scales for the assessment of severity grading.

AEs were protocol-defined as: “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 is considered associated (i.e., adverse drug reaction [ADR]) with the use of the drug if the attribution is possible, probable, or very likely.

Serious AEs (SAEs) were protocol-defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important

Based on signals from nonclinical toxicity studies or previously identified potential NNRTI-class effect, adverse of events of interest for further safety evaluation included hypersensitivity reactions and rash, neuropsychiatric events, hepatic events, endocrine events, and potential QT-prolongation-related events.

7.3.3. Reviewer's Approach to the Safety Evaluation

The review approach for assessment of risk consisted of evaluating the safety data from Studies C213 Cohort 2 and HTX2002, and the cumulative safety data that are available from adolescents and adults. Studies C213 and HTX2002 were reviewed separately because the studies enrolled different patient populations. Study 2C13 included an ARV treatment-naïve population, while Study HTX2002 enrolled a virologically-suppressed population. Clinical study data from Studies C213 and HTX2002 were independently analyzed using JMP v.16.2.0 and AnalysisStudio v1.8.0. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

7.4. Adequacy of the Clinical Safety Database

A total of 44 pediatric participants from Studies C213 Cohort 2 and HTX2002 provided a reasonable assessment of safety through Week 48 in children at least 2 years of age and weighing at least 14 kg. Of note, only one participant was less than 6 years of age, and five participants weighed less than 20 kg. We acknowledge that there are limited safety data in participants <6 years of age or <20 kg from Studies C213 and HTX2002; however, based on the totality of the use-experience of RPV and the safety database for children, adolescents, and adults, there was no reason to expect the safety profile in children 2 to <6 years of age to be different from older populations. RPV has an established safety profile and has been approved in adults since 2011 and in adolescents since 2015. As previously noted, additional safety and PK data for RPV from children at least 2 years of age and weighting at least 10 kg are expected from the ongoing phase 1/2 study, IMPAACT 2036 (CRAYON).

7.5. Safety Findings and Concerns Based on Review of Clinical Safety Database

The Applicant submitted safety data from a total of 44 pediatric participants; 18 participants were enrolled in Study C213 Cohort 2 and 26 participants were enrolled in Study HTX2002 (all received at least one dose of RPV). Studies C213 and HTX2002 were not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences. Descriptive statistics were therefore applied to describe the observed findings.

The demonstrated safety profile of RPV in participants with HIV-1 infection is acceptable at the indicated weight-adjusted doses. No new safety concerns emerged that were not apparent with the known safety profile of RPV. Only treatment-emergent events (TEAEs) are described in the below subsections.

7.5.1. Safety Findings from Study C213 Cohort 2 and Study HTX2002

Study C213:

The completed phase 2 Study C213 Cohort 2 was conducted to evaluate the PK, safety, tolerability, and efficacy (antiviral activity) of RPV in ARV treatment-naïve children ≥6 to <12 years of age with a body weight ≥17 kg. Of the 18 participants enrolled in Study C213 Cohort 2, 17 of 18 (94%) participants completed the 48-week treatment period and 12 of 18 (67%) participants entered the post-Week 48 treatment extension period. The median duration of exposure for participants in the Week 48 analysis (including post-Week 48 extension) was 69.5 weeks (range: 34.9 to 218.3 weeks).

Study HTX2002:

The completed phase 2 study HTX2002 was conducted to evaluate the PK, safety, tolerability, and antiviral activity/efficacy of RPV in combination with other ARVs in virologically-suppressed children ≥2 to <12 years of age with a body weight of ≥10 kg. At the final analysis, all 26 participants enrolled had completed the Week 48 visit; none of the participants terminated the study prematurely. The median duration of exposure for participants in the Week 48 analysis was 48.4 weeks (range: 47.0 to 52.3 weeks).

7.5.1.1. Deaths

No deaths were reported in the 48-week treatment period for Studies C213 and HTX2002, and in the post-Week 48 treatment extension period for Study 213.

7.5.1.2. Serious Adverse Events

No SAEs were reported in the 48-week treatment period for Studies C213 and HTX2002, and in the post-Week 48 treatment extension period for Study 213.

7.5.1.3. Dropouts and/or Discontinuations Due to Adverse Events

No AEs leading to drug discontinuation were reported in the 48-week treatment period for Studies C213 and HTX2002, and in the post-Week 48 treatment extension period for Study 213.

7.5.1.4. Treatment-Emergent Adverse Events

Study C213:
Overall, 17 of 18 (94%) participants experienced AEs in the 48-week treatment period, and 7 of 12 (58%) participants experienced AEs in the post-Week 48 treatment extension period. No ≥Grade 3 AEs were reported in the 48-week treatment period and in the post-Week 48 treatment extension period. A summary of all AEs from the 48-week treatment period and the post-Week 48 treatment period of Study C213 is included in Section III.15.

Common Adverse Events

In the 48-week treatment period, the most commonly reported AEs (≥2 participants) were upper respiratory tract infection (12 participants; 67%), and otitis media, decreased appetite, anemia, diarrhea, vomiting, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, cough, and rash (2 participants each, 11%). All other AEs were reported in one participant only. Upper respiratory tract infection was the only AE reported in more than 1 participant in the post-Week 48 extension period, with 5 of 12 (42%) participants reporting this AE.

Adverse Drug Reactions

Overall, 1 of 18 (6%) participants experienced an ADR that was at least possibly related to RPV by the investigator. This participant was in the ≥25 kg dose-weight group (25 mg PO QD) and the events occurred during the 48-week treatment period. The ADRs experienced by this participant included non-serious (Grade 1) increases in ALT and AST on Day 25. No action was taken as a result of the events, and the events did not lead to treatment discontinuation. The events resolved spontaneously during the 48-week treatment period (Day 60), and the participant continued receiving RPV and rolled over to Study IFD3004. No other AEs were considered by the investigator to be at least possibly related to RPV or the background regimen in Study C213 Cohort 2.

Study HTX2002:

Overall, 19 of 26 (73%) participants had at least 1 AE during the 48-week study period. Most of the AEs were Grade 1 in severity and no ≥Grade 3 AEs were reported in the 48-week treatment period. A summary of all AEs during the 48-week treatment period of Study HTX2002 are included in Section III.15.

Common Adverse Events

In the 48-week treatment period, the most commonly reported AEs (≥2 participants) were vomiting (4 participants; 15%), ALT increased (3 participants; 12%), abdominal pain, AST increased, decreased appetite, headache, nasal congestion, nausea, pyrexia, rhinitis, and upper respiratory tract infection (2 participants each; 8%).

Adverse Drug Reactions

A total of 6 ADRs in 3 of 26 (12%) participants were reported to be at least possibly related to RPV by the investigator. All 6 ADRs were Grade 1 in severity and none of the ADRs led to treatment discontinuation.

- One participant (15 to <20 kg group) experienced Grade 1 vomiting. No action was taken with regard to study medication, no treatment was reported for the event, and the event resolved.
- One participant (≥25 kg group) experienced Grade 1 abdominal pain. No action was taken with regard to study medication, no treatment was reported for the event, and the event did not resolve.
- One participant (≥25 kg group) experienced Grade 1 nausea (not resolved), vomiting (resolved), cortisol decreased (resolved; see Section 7.5.1.5), and folate deficiency (resolved).

7.5.1.5. Adverse Events of Interest

Study C213:

AEs of interest were reported in a total of 8 of 18 (44%) participants during the study; 6 of 18 (33%) participants had AEs of interest in the 48-week treatment period, and 2 of 12 (17%) participants had AEs of interest during the post-Week 48 treatment extension period. The majority of these events were reported in the 25 mg QD (<25 kg) or in the 25 mg QD (≥25 kg) dose-weight groups. The AEs of interest are described below.

Study HTX2002:

AEs of interest were reported in a total of 11 of 26 (42%) participants in the 48-week treatment period. Most of the AEs of interest were Grade 1 in severity and all were considered not related to the study intervention by the investigator except for the AE of cortisol decreased. Most of these events were reported in the ≥25 kg dose-weight group. The AEs of interest are described below.

Hypersensitivity reactions/rash

Study C213:

A total of 4 of 18 (22%) participants experienced an AE of hypersensitivity reaction/rash.

48-week treatment period

- Two participants experienced Grade 1 rash; one participant in the 15 to 25 kg group (onset Day 16, resolved Day 83), and the other participant in the ≥25 kg group (onset Day 78, resolved Day 80). Both events resolved and were assessed as not related to RPV by the investigator.
- One participant (20 to <25 kg group) experienced Grade 1 atopic dermatitis (onset Day 1, resolved Day 13). The event resolved and was assessed as not related to RPV by the investigator.

Post-Week 48 treatment extension period

- One participant (20 to <25 kg group) experienced Grade 2 dermatitis (onset Day 498, resolved Day 505). The event resolved and was assessed as not related to RPV by the investigator.

Study HTX2002:

A total of 2 of 26 (8%) participants experienced an AE of hypersensitivity reaction/rash.

- One participant (≥25 kg group) experienced Grade 1 rash on Day 98. The participant received treatment with topical and oral chlorpheniramine. No action was taken with regard to the study medication because of this event. The AE of rash was reported as resolved on Day 103 and was assessed as not related to RPV by the investigator.
- One participant (≥25 kg group) experienced Grade 1 erythema on Day 290. No treatment was reported for this event, and no action was taken with regard to the study medication because of this event. The AE of erythema was reported as resolved on Day 295 and was assessed as not related to RPV by the investigator.

Neuropsychiatric events

Study C213:

A total of 1 of 18 (6%) participants experienced an AE describing a neuropsychiatric event.

48-week treatment period

- No events.

Post-Week 48 treatment extension period

- One participant (≥25 kg group) experienced Grade 1 depression (onset Day 926, resolved Day 1093). The event resolved and was assessed as not related to RPV by the investigator.

Study HTX2002:

A total of 6 of 26 (23%) participants experienced an AE describing a neuropsychiatric event.

- One participant (20 to <25 kg group) experienced Grade 1 headache on Day 3. No treatment was reported for this event, and no action was taken with regard to the study medication because of this event. The AE of headache was reported as resolved on Day 4 of treatment with the study medication and was assessed as not related to RPV by the investigator.
- One participant (≥25 kg group) experienced Grade 1 headache on Day 154. The participant received treatment with paracetamol for this event. No action was taken with regard to study medication because of this event. The AE of headache was reported as resolved on the same day and was assessed as not related to RPV by the investigator.
- One participant (≥25 kg group) experienced Grade 1 somnolence on Day 50. No treatment was reported for this event, and no action was taken with regard to study medication because of this event. The AE of somnolence was reported as resolved on Day 113 and was assessed as not related to RPV by the investigator.
- One participant (≥25 kg group) experienced Grade 1 dizziness on Day 29. No treatment was reported for this event, and no action was taken with regard to the study medication because of this event. The AE of dizziness was reported as resolved on Day 32 and was assessed as not related to RPV by the investigator.
- One participant (≥25 kg group) experienced Grade 1 amnesia on Day 70. No treatment was reported for this event, and no action was taken with regard to the study medication because of this event. The AE of amnesia was reported as resolved on Day 100 and was assessed as not related to RPV by the investigator.
- One participant (≥25 kg group) experienced Grade 1 attention deficit hyperactivity disorder on Day 72. No treatment was reported for this event, and no action was taken with regard to study medication because of this event. The AE of attention deficit hyperactivity disorder was reported as resolved on Day 171 and was assessed as not related to RPV by the investigator.

Hepatobiliary events

Study C213:

A total of 2 of 18 (11%) participants experienced an AE describing a hepatobiliary event.

48-week treatment period

- Two participants experienced Grade 1 increase in AST and ALT; one participant in the 20 to <25 kg group (onset Day 34, resolved Day 55), and the other participant in the ≥25 kg group (onset Day 25, resolved Day 60). Both events resolved; however, the events of increased AST and ALT were assessed by the investigator as related in one participant (no action was taken as a result of the events and the events resolved spontaneously during the 48-week treatment period while still receiving RPV).

Post-Week 48 treatment extension period

- No events.

Study HTX2002:

A total of 3 of 26 (12%) participants experienced an AE describing a hepatobiliary event.

- One participant (≥25 kg group) experienced AEs of Grade 2 ALT increased and Grade 1 AST increased on Day 192. No treatment was reported for these events. No action was taken with regard to the study medication due to these events. The investigator considered these AEs to be not related to the study medication and the participant's background regimen. Approximately one month later, the AE of ALT increased improved to Grade 1 in severity, and a Grade 1 AE of gamma-glutamyltransferase increased was reported. No treatment was reported for this event. No action was taken with regard to the study medication because of this event.
- One participant (≥25 kg group) experienced a Grade 2 AE of ALT increased on Day 28. No treatment was reported for this event, and no action was taken with regard to the study medication because of this event. The AE of ALT increased was reported as resolved on Day 45 of treatment with the study medication and was assessed as not related to RPV by the investigator. On Day 112, a Grade 2 AE of ALT increased was reported. No treatment was reported for this event, and no action was taken with regard to the study medication because of this event. The AE of ALT increased was reported as resolved on Day 141 and was assessed as not related to RPV by the investigator.
- One participant (≥25 kg group) experienced Grade 1 AEs of ALT increased and AST increased on Day 30. No treatment was reported for these events, and no action was taken with regard to the study medication because of these events. Both events of AST increased and ALT increased were reported as resolved at the time of the Week 40 visit and were assessed as not related to RPV by the investigator.

Endocrine events

As previously mentioned, due to nonclinical signal observed that suggested RPV may partially inhibit 17-hydroxylase, the clinical development programs included careful assessment for adrenal-related adverse events. During the adult and adolescent trials, the following evaluations were included to assess the hypothalamic-pituitary-adrenal (HPA) axis function:

> **ACTH stimulation test:** was conducted routinely at Weeks 0 and 48. Cortisol (17-OHP), and aldosterone were measured before (0 minutes), 30 and 60 minutes after ACTH stimulation. If the ACTH stim test result were abnormal (i.e., cortisol values <500 nmol/L), a retest was performed at the next scheduled visit.
>
> **Basal cortisol level:** drawn at Weeks 0, 4, 12, 24, 48, and 96. If at any time point the value were <248 nmol/L, a retest was done at the subsequent visit (approximately within

the following 8 weeks). If basal cortisol level were <248 nmol/L at two consecutive visits, an ACTH stimulation test was conducted at the next scheduled visit, as described above.

Subject withdrawal was considered in participants who failed a repeat ACTH stimulation test *and* had clinical signs/symptoms of adrenal insufficiency (i.e., 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/or hirsutism).

Based on the overall reassuring results from the adult and adolescent trials, the pediatric protocol (C213) was amended (Amendment 10): the ACTH stimulation test at baseline and Week 24 was replaced by reflex testing (i.e., ACTH stimulation test was to be performed in case of confirmed low cortisol (<248 nmol/L [9 µg/dL]) or in case of signs or symptoms of adrenal insufficiency. If the ACTH stimulation test was abnormal (i.e., the cortisol value after ACTH stimulation was <500 nmol/L [18.1 µg/dL]), a retest was to be performed at the next scheduled visit or at least within the next 8 weeks, with measurements of cortisol and 17-hydroxyprogesterone.

***Endocrine-related clinical AEs, as assessed by the investigator**:*

Among the pediatric participants enrolled in Studies C213 and HTX2002, there were no discontinuations because of low serum cortisol level or because of signs and symptoms of adrenal insufficiency.

Study C213:

A total of 1 of 18 (6%) participants experienced an AE describing an endocrine event.

48-week treatment period

- One participant (≥25 kg group) experienced a Grade 1 abnormal ACTH stimulation test (onset Day 1). The event did not resolve and was assessed as not related to RPV because of the very short latency between starting study medication and the event. No action was taken with regard to study medication and no treatment was reported for the event. The participant did not have clinical signs of adrenal insufficiency, and no electrolyte disturbances were reported during the study. In addition, no AEs of decreased blood cortisol were reported. This participant is further described in Section 7.5.3.1.

Post-Week 48 treatment extension period

- No events.

Study HTX2002:

A total of 1 of 26 (4%) participants experienced an AE describing an endocrine event.

One participant (≥25 kg group) experienced a Grade 1 AE of cortisol decreased on Day 169. No treatment was reported for this event, and no action was taken with regard to study medication because of this event. The AE of cortisol decreased was reported as resolved on Day 191, while still receiving study medication. No clinical

symptoms suggestive of an endocrine event were noted. The investigator considered this AE to be possibly related to RPV and the background regimen.

Basal cortisol levels and any ACTH stim test results

Study C213:

Baseline basal cortisol level was normal for 4 of 18 (22%) participants, low for 13 of 18 (72%) participants, and missing for 1 of 18 (6%) participants.

Among the four participants with normal basal cortisol at baseline, three participants had either normal basal cortisol levels (≥248 nmol/L) or normal cortisol levels 1 hour after ACTH stimulation (≥500 nmol/L) throughout the study and/or at the last available visit (Week 24 and Week 72). One participant had low basal cortisol at the last available assessment (Week 48) and no ACTH stimulation test was performed. For this participant, laboratory AEs of anemia and hypokalemia were reported with onset date 6 days after start of RPV treatment; both events were Grade 1, considered by the investigator as not related to RPV, and resolved by the time of the Week 2 visit. No additional AEs suggestive of adrenal insufficiency were reported for this participant.

Among the 13 participants with low basal cortisol predose on Day 1, 2 participants had low basal and ACTH stimulated cortisol values throughout the study, including ACTH stimulated cortisol at baseline before starting treatment with RPV. One of these two participants had an AE of ACTH stimulation test abnormal reported at baseline which was considered by the investigator as not related to RPV or the background regimen and was ongoing at the end of study. For both participants, no AEs suggestive for adrenal insufficiency were reported. The remaining 11 participants had normal serum cortisol values after ACTH stimulation at baseline and/or during treatment (at Week 24 per protocol up to Amendment 9, or at later assessments during the study).

Study HTX2002:

As of Protocol Amendment 2, ACTH stimulation test had to be performed in participants ≥6 to <12 years who had (confirmed) abnormally low basal cortisol levels (<248 nmol/L [9 μg/dL]) or signs or symptoms of adrenal insufficiency. Prior to Amendment 2, ACTH stimulation test was performed at Day 1 and Week 24 (in participants ≥6 to <12 years). Cortisol and 17-hydroxyprogesterone were measured before and 1 hour after ACTH stimulation.

Overall, 15 of 26 (58%) participants had normal baseline cortisol levels, either basal or 60 minutes after ACTH stimulation testing, 9 of 26 (35%) participants had low (<248 nmol/L) basal cortisol levels on Day 1 before starting RPV treatment, and 2 of 26 (8%) participants had missing baseline values.

At Week 48, 6 participants had normal basal cortisol levels (≥248 nmol/L) and 19 participants had low basal cortisol levels (Week 48 result was not available for 1 participant).

- In 15 of the 19 participants with low basal cortisol, the Week 48 serum cortisol levels returned to normal (≥248 nmol/L) after repeat serum basal cortisol testing

or was normal after ACTH stimulation testing (≥500 nmol/L). No AEs suggestive of adrenal insufficiency were reported in these 15 participants.

- In 4 of the 19 participants with low basal cortisol, the serum cortisol levels remained low after repeat serum basal cortisol testing or after ACTH stimulation testing. One of those participants (≥20 to <25 kg dose-weight) had consistent ACTH-stimulated cortisol values between 400 to 500 nmol/L during the study after normal ACTH-stimulated cortisol value at baseline. No adrenal-related AEs were reported for this one participant.

As previously noted, one participant with normal cortisol levels at baseline and Week 48 (repeat basal value) had a Grade 1 AE of cortisol decreased reported at Week 24, which was assessed by the investigator as possibly related to RPV and background regimen. Repeat testing 3 weeks later showed that the basal cortisol was normal again (≥248 nmol/L) and the event resolved while the participant was still receiving RPV and background regimen.

Potential QT-prolongation-related events

Study C213:

A total of 1 of 18 (6%) participants experienced an AE describing a potential QT-prolongation-related event.

48-week treatment period

- One participant (≥25 kg group), whose baseline QTcB and QTcF were recorded as 440 msec and 398 msec, respectively, experienced two events of ECG QT prolonged (Grade 1 [456 msec] onset Day 163, not resolved; Grade 2 [469 msec] onset Day 88, resolved Day 115). Both AEs were associated with a prolonged QTcB interval; however, all reported QTcF intervals were normal (<440 msec) at all timepoints throughout the study. No action was taken with regard to study medication and no treatment was reported for the event. The events resolved and were assessed by the investigator as not related to RPV.

Post-Week 48 treatment extension period

- No events.

Study HTX2002:

A total of 1 of 26 (4%) participants experienced an AE describing a potential QT-prolongation-related event.

- One participant (15 to <25 kg group), whose baseline QTcB and QTcF were 410 msec and 387 msec, respectively, experienced a Grade 2 AE of ECG QT prolonged (QTcB) on Day 162 (QTcF interval at 440 msec). No treatment was reported for this event and no action was taken with regard to the study medication due to this event. The AE of ECG QT prolonged (QTcB) was reported as resolved on Day 199 (QTcF interval at 400 msec).

7.5.2. Laboratory Findings, Study C213 Cohort 2 and Study HTX2002

Study C213:

Overall, no clinically meaningful changes in laboratory parameters were noted. Most treatment-emergent laboratory abnormalities were Grade 1 and there were no Grade 4 laboratory abnormalities.

Four of 18 (22%) participants had Grade 3 treatment-emergent laboratory abnormalities and are briefly summarized below (none of these laboratory abnormalities were reported as an AE):

- One participant in the ≥25 kg dose-weight group was observed with Grade 3 amylase increased at Week 12 that decreased to Grade 2 at Week 16. Amylase values at later time points were Grade 1 (Week 24 and Week 32) and then normal starting at Week 40. Concomitant ARVs included 3TC and AZT.
- One participant in the ≥25 kg dose-weight group was observed with Grade 3 neutrophils and precursors decreased at Week 24 with a normal value at baseline; the value returned to Grade 2 at Weeks 32 and 40, and normal at Week 48. Concomitant ARVs included 3TC and AZT.
- One participant in the ≥25 kg dose-weight group was observed with Grade 3 estimated glomerular filtration rate (eGFR) decreased at Week 24 with a normal value at baseline; the value returned to Grade 2 at Week 32. Concomitant ARVs included ABC and 3TC.
- One participant in the <20 kg dose-weight group was observed with Grade 3 eGFR decreased at Week 1 with a normal value at baseline; the value returned to Grade 2 from Week 2 and remained Grade 2 until Week 40. Concomitant ARVs included ABC and 3TC.

Study HTX2002:

Overall, no clinically meaningful changes in clinical laboratory values were reported up to Week 48. Most laboratory values were Grade 1, and there were no Grade 4 abnormalities.

Three of 26 (12%) participants had Grade 3 treatment-emergent laboratory abnormalities and are briefly summarized below (none of these laboratory abnormalities were reported as an AE):

- One participant in the ≥25 kg dose-weight group was observed with a Grade 3 abnormality of neutrophils and precursors decreased at Week 40; however, results were reported as normal at Week 32 and Week 48 (Baseline results were Grade 1).
- One participant in the ≥25 kg dose-weight group was observed with a Grade 3 abnormality of eGFR (based on a >30% change from baseline) at Week 4 and Week 48 (and Grade 2 at all other time points). Absolute eGFR values were normal at all available time points.
- One participant in the ≥25 kg dose-weight group was observed with a Grade 3 abnormality of eGFR (based on a >30% change from baseline) at Week 8 and subsequently remained at Grade 2 through Week 48. Absolute eGFR values were normal at all available time points.

7.5.3. Other Safety Evaluations

7.5.3.1. Study C213 Cohort 2 and Study HTX2002

Study C213:

There were no clinically meaningful findings in the vital signs measurements, physical examination assessments (including growth and pubertal development assessed by Tanner staging), or other observations related to safety in this study.

Study HTX2002:

Similarly, there were no clinically meaningful findings in the vital signs measurements, physical examination assessments (including growth and pubertal development assessed by Tanner staging), or other observations related to safety in this study.

7.5.3.1.1. Electrocardiograms

Study C213:

All QTcF values were normal (<460 msec) in all participants at all timepoints, and none of the participants had increases in QTcF from baseline >60 msec. Three of 18 (17%) participants had a worst increase in QTcF from baseline of 30 to ≤60 msec in QTcF; however, all QTcF values were <460 msec. No clinically relevant abnormalities were reported for other ECG parameters (HR, PR, QRS, and RR interval).

Study HTX2002:

All QTcF values were normal (<460 msec) in all participants at all timepoints, and none of the participants had increases in QTcF from baseline of >60 msec. Three of 26 (12%) participants had a worst increase of 30 to 60 msec from baseline in QTcF; however, all QTcF values were <460 msec. No clinically relevant abnormalities were reported for other ECG parameters (HR, PR, QRS, and RR interval).

7.5.3.1.2. Physical Examination Findings

Study C213:

There were no clinically meaningful findings in the physical examination assessments (including growth and pubertal development). As expected in this population, increases in height and weight were observed over the 48-week treatment period. At Week 48, the mean (SD) increase from baseline in height and weight was 6.1 (2.8) cm and 2.5 (2.4) kg.

At Week 48, Tanner stage for genitalia remained stage I for 9/12 male participants as at Baseline and increased to stage II and III in 1 participant each. At Week 48, Tanner stage for breasts remained stage I for 2/7 female participants and stage 2 for 2/7 female participants as at baseline. In 1 participant Tanner stage increased to stage 2 at Week 48.

Study HTX2002:

There were no clinically meaningful findings in the physical examination assessments (including growth and pubertal development). As expected in this population, increases in height and weight were observed over the 48-week treatment period. At Week 48, the mean (SD) increase from baseline in height and weight was 5.9 (1.8) cm and 4.4 (2.8) kg.

In male participants in the ≥6 to <12 years age group, 12 participants were in Tanner Stage I and 4 were in Stage II for genitalia development at baseline. At Week 48, eight participants remained in Stage I, 3 were in Stage II, and 1 was in Stage III. In one 8-year-old participant, Tanner stage for genitalia changed from I at baseline to III at Week 24 and remained at III at Week 48. In this participant, pubic hair stayed at Stage I from baseline through Week 48. No AEs related to adrenal insufficiency or cortisol abnormalities were reported for this participant. All basal cortisol levels were normal, and no reflex ACTH stimulation testing was required for this participant throughout the study. One of the four participants in Stage II at baseline for genitalia development changed to Stage III at Week 48, the other three participants remained in Stage II. For pubic hair development, among the 13 male participants who were in Stage I at baseline, 10 remained in Stage I and 3 were in Stage II at Week 48 . Among the three participants who were in Stage II at baseline, two remained in Stage II and one was in Stage III at Week 48.

In female participants in the ≥6 to <12 years age group, all four participants who were in Tanner Stage I for breast development at baseline remained in the same stage at Week 48. All three participants who were in Stage II at baseline were in Stage III at Week 48. For pubic hair, among the five participants who were in Stage I at baseline, four remained in Stage I and one was in Stage II at Week 48. Three of the 4 participants who were in Stage II at baseline were in Stage III at Week 48. Only one 11-year-old girl had a date of first menses reported during the study (on Day 81 since first RPV intake).

7.5.4. Safety Update Report

On July 14, 2023, the Sponsor submitted a Periodic Benefit-Risk Evaluation Report (PBRER) covering post-marketing safety assessment for the review period beginning May 20, 2022, through May 19, 2023. In the PBRER, the Applicant concluded that there were no new data that modified the benefit-risk profile of RPV in the approved indication during the reporting period. In addition, the Applicant noted that there were no new important potential risks or safety concerns were identified for RPV during this reporting period, and there were no new safety data or efficacy data that had meaningfully altered the overall benefit-risk profile for the approved indication.

The Applicant submitted a 120-Day Safety Update Report of Study IFD3004 and postmarketing safety data from May 20, 2023, up to September 20, 2023, which covers the 4-month period since May 19, 2023. As previously mentioned, Study IFD3004 is a phase 2, open-label, roll-over, multicenter study with oral RPV in pediatric participants who participated in the RPV pediatric Studies C213 and HTX2002. Study IFD3004 provides continued access of RPV to participants that are expected to continue experiencing benefit from treatment with RPV. Of the 17 participants who completed the 48-week treatment period in Study C213 Cohort 2, five participants rolled over to Study IFD3004 at Week 48, and eight participants rolled over to Study IFD3004 after Week 48. Of 26 participants who completed the Week 48 visit in Study

HTX2002, 21 participants rolled over to Study IFD3004 after completing Week 48. No new safety concerns were identified in the 120-Day Safety Update Report and the provided postmarketing safety data.

7.6. Key Review Issues Relevant to Evaluation of Risk

7.6.1. Resistance Assessments of Virologic Failures

Issue

A high rate of virologic failure was identified in Study C213 Cohort 2, which raises concern about emergence of resistance to RPV and other NNRTIs.

Background

A single viral substitution can confer high-level drug resistance to all NNRTIs, and cross-resistance to other NNRTIs is common.

Assessment

Study C213 Cohort 2 (ARV treatment-naïve, adolescents with HIV-1 infection aged 6 to <12 years)

Genotypic and Phenotypic Analysis at Screening/Baseline
Plasma-based deep sequencing analysis was planned at screening or baseline for all 18 participants and was successful for 17/18 participants. A whole blood sample was available for eight participants at screening and retrospective archived resistance testing data were available for all of them. Four of these eight participants carried the archived NNRTI polymorphism V179I; this substitution was also observed through standard plasma-based resistance testing in each of these participants. Two out of four participants with archived V179I had undetectable HIV-1 viral load at Week 48 while one subject had 55 copies/mL at Week 48 and one subject had missing data in window. In addition, one participant had archived NNRTI resistance substitution K101K/Q, and one participant had archived NRTI resistance substitution M184M/I at screening. The participant with pre-existing K101K/Q did not reach undetectable plasma viral load (<50 copies/mL) and withdrew from the study at Week 32. The participant with archived M184I/M at screening had undetectable HIV-1 viral load from Week 12 onwards.

According to the phenotypic analysis at screening and baseline, all 18 participants were susceptible to RPV and all were susceptible to their NRTI backbone regimen.

Definition of Virologic Failure
Participants were to be classified according to the below definitions. Viral load cut-offs of 200 or 400 copies/mL were used instead of 50 copies/mL, as these viral loads are associated with the

minimum level of circulating virus needed for successful plasma-based standard resistance testing.

- Virologic failure
  - Lack of response: confirmed decrease in plasma viral load of <1.0 $\log_{10}$ at Week 12 from the baseline viral load
  - Loss of response: 2 consecutive measurements of ≥400 copies/mL after having been confirmed virologic responder; confirmed responder is defined as 2 consecutive measurements of <50 copies/mL
- Suspected virologic failure: ≥200 copies/mL after confirmed plasma viral load of <50 copies/mL

Post-baseline Genotypic and Phenotypic Data

Six out of 18 (33%) participants had at least one visit with post-baseline standard genotypic data within the treatment phase; two of these visits occurred within the first 48 weeks and four occurred post-Week 48. Of these six participants, five participants had phenotypic data available at the first and last time point with post-baseline genotypic data. Five of these participants had available viral load data at baseline, two of whom had a baseline viral load ≥100,000 copies/mL. There were two other participants, Participants (b) (6) and (b) (6), with >100,000 copies/mL at Baseline who achieved and remained <20 copies/mL out to Week 192 and Week 60, respectively.

In the FDA resistance analysis, six participants were considered virologic failures (Table 16). Three participants were <25kg and three were >25 kg. Of the six virologic failures, five had treatment-emergent RPV resistance-associated substitutions [K101E (n=3), E138Q or K (n=3), Y181C (n=1), H221Y (n=2), P225P/L (n=1), M230M/L (n=1)], four of whom also had decreased RPV susceptibility phenotypically. These emergent RPV resistance-associated substitutions in pediatric patients are consistent with those seen in adults failing on an RPV-containing regimen. In addition to RPV resistance, four of the virologic failure participants also had treatment-emergent resistance substitutions to other drugs in the regimen [M184V (n=3) and M184M/I (n=1) conferring decreased susceptibility to 3TC; M41L (n=1) conferring decreased susceptibility to AZT; and K65R/Y115F (n=1) conferring decreased susceptibility to ABC].

Two participants ((b) (6)) with reported suboptimal adherence and post-baseline genotypic data experienced virologic failure at Week 72 (Table 16).

Table 16. Resistance Emergence in Virologic Failures, Study C213 (n=6/18, 33%)

PID	Screening/ Baseline Viral Load	Wt/Dose QD	Failure Timepoint/HIV-1 RNA copies/mL	Emergent Genotypic RAS	Fold Change at Failure
(b) (6)	55400/57800	<25 kg/25 mg	WK48/703	K101K/E E138Q V179V/I M184V P225P/L	**RPV 4.1** AZT 0.7 **3TC 109**
	22600/32500	<25 kg/25 mg	WK132/15200	none	RPV 0.83 AZT 0.68 3TC 0.96
	85300/121000	>25 kg/25 mg	WK120/303	M41L E138K M184V H221Y	**RPV 7.6** AZT 1.5 **3TC 145**
	56600/33900	>25 kg/25 mg	WK72/1710	V90V/I E138E/K/A/G M184V M230M/L	**RPV 14** AZT 1.4 **3TC 145**
	52700/133000	<25 kg/25 mg	WK72/11800	K101K/E E138K/E/Q H221H/Y	RPV 2 TDF 0.8 3TC 1.3
	-/34500	>25 kg/25 mg	WK24/1150 WK32/2690	K65R K101E Y115F Y181I M184M/I	**RPV 41, 115 ABC** 2.6**, 8.4 3TC 141**

[a] Baseline HIV-1 RNA>100,000 copies/mL.
[b] Suboptimal adherence (>95% pill count).
Bolded = decreased susceptibility.
PID, participant identification number; RAS, resistance-associated substitutions; QD, once daily.

The available adherence information together with popPK parameters for each of the six participants are summarized in Table 17.

Table 17. Adherence and PK for C213 Virologic Failures

Participant ID	RPV Pill count at Week 48 (%)	RPV Pill count using all data (%)	Adherence Questionnaires Summary	RPV AUC_{24h} (ng.h/mL)	RPV C_{trough} (ng/mL)
(b) (6)	96.4	96.9	RPV: No doses missed	2667	94.0
	94.9	98.1	RPV: No doses missed	4704	161
	93.2	98.8	RPV: 1 dose missed at Week 12, Combivir: 6 doses missed at Week 12	2567	88.8
	98.8	89.6	RPV: No doses missed	2318	82.5
	79.9	88.4	RPV: No doses missed	4749	162
	99.6	99.6	RPV: No doses missed, ABC/3TC: 1.5 doses missed at Week 24	4394	150

Source: Listings lsiadh01 and lsiadh02, PopPK report - Appendix 20 (EDMS-RIM-928244)

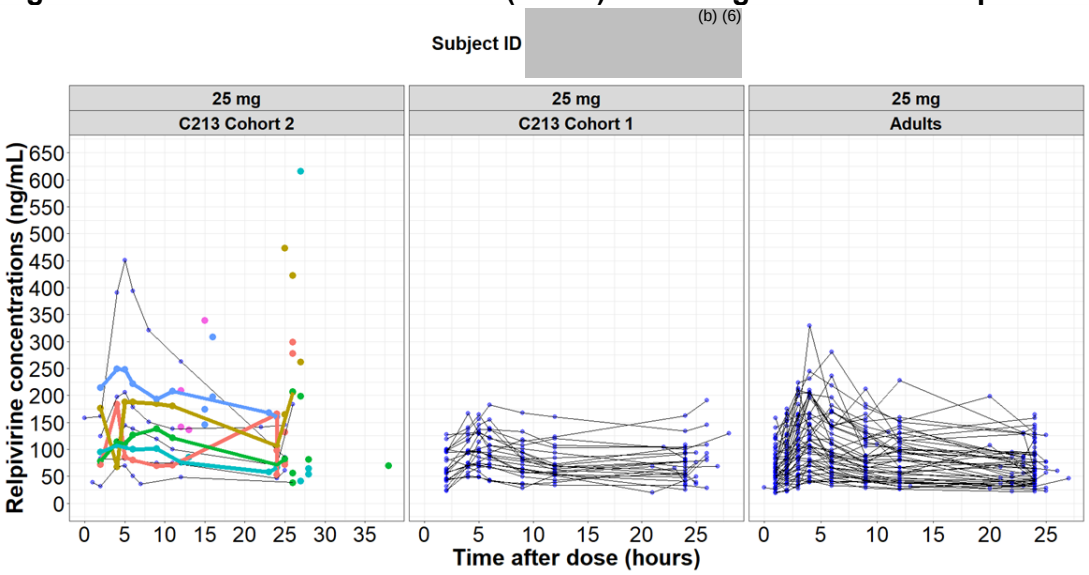
Pharmacokinetics (PK) of Virologic Failures

In Study C213 Cohort 2, the six participants who were virologic failures had exposures comparable to adults at the approved dose. The concentrations over time in the six virologic failure participants were higher or comparable to the adult cohort (Table 17 and Figure 2).

Concentrations versus time graphs, after the inclusion of the Sparse PK samples (dots not linked with a solid line) from the six participants with VF in C213 Cohort 2 are shown in Figure 2.

The PK data cannot exclude virologic failure due to lack of adherence. For the C213 Cohort 2, the rich PK sampling was performed at Week 2 and 3, as indicated in the protocol (Week 2). In the PK data, sparse PK was collected between 4 to 48 for most participants with virologic failure.

Figure 2. Concentrations Over Time (hours) in Virologic Failure Participants



Bold solid lines are the rich PK profile per day (Week 2 to 3) in participants with VF.
Thin solid lines are the rich PK profile per day for all other participants.

Study C213 Cohort 1 (ARV treatment-naïve, adolescents with HIV-1 infection aged ≥12 to <18 years)

Data on Cohort 1 were previously submitted in NDA202022 SDN217 (sequence 106). The Applicant agreed to add resistance information on Cohort 2 (reviewed above) in Section 12.4 of the USPI but proposed to also include a summary of adolescent Cohort 1 resistance data. At the time of the C213 Cohort 1 analysis reviewed in 2015, resistance data were not included in the USPI because no new resistance substitutions were identified, and the adult resistance data were deemed adequate to inform the prescriber. However, the Division is now including resistance data from Cohort 2 in Section 12.4 of USPI, because of the high rate of virologic failure and resistance emergence. Thus, Cohort 1 resistance information will also be included in Section 12.4 of the USPI for completeness.

The Cohort 1 resistance information is summarized below:

For participants in the baseline viral load category ≤100,000 copies/mL (N=28), at Week 48, 5/28 (18%) participants were considered virologic failures. For participants in the baseline viral load category >100,000 copies/mL (N=8), at Week 48, 3/8 (38%) participants were considered virologic failures.

Baseline Resistance Analysis
For all 36 participants, genotypic data were available at baseline and/or screening. Phenotypic data were available for 34/36 (94%) participants at baseline. None of the participants carried RPV resistance-associated substitutions or NRTI resistance-associated substitutions at baseline. While 32/34 (94%) participants were susceptible to RPV according to phenotypic analysis at baseline, 2/34 (6%) subjects had a baseline RPV fold change value ≥2.5-fold. One of these 2 participants experienced virologic failure. The majority of participants (64%) were infected with HIV-1 clade C.

Analysis of Virologic Failures
Eight of 36 (22%) participants experienced virologic failure in the first 48 weeks (four participants 'never suppressed' and four participants rebounded); two participants discontinued due to other reasons than virologic failure (1 due to an AE and 1 due to other reasons). Four additional participants experienced virologic failure (rebound) after their Week 48 visit.

Genotypic Analysis
Of the eight participants with virologic failure and post-baseline genotypic data, five (63%) had at least one treatment-emergent RPV resistance-associated substitution. The RPV resistance-associated substitutions detected in these five participants were E138K (n=4), K101E (n=2), M230L (n=2), E138G (n=1), E138R (n=1), Y181I (n=1), and H221Y (n=1). In four of these five with treatment-emergent RPV resistance-associated substitutions, at least one treatment-emergent NRTI resistance-associated substitution was also observed at failure. These substitutions were M184V (n=3), K65R (n=1), and Y115F (n=1). The two participants who discontinued due to other reasons than virologic failure did not have treatment-emergent NNRTI or NRTI resistance-associated substitutions. Finally, none of the four participants with virologic failure after their Week 48 visit had treatment-emergent NNRTI or NRTI resistance-associated substitutions.

Phenotypic Analysis
For three of five (60%) participants experiencing virologic failure with treatment-emergent RPV resistance-associated substitutions, the RPV fold change value was >2.5-fold at the last post-baseline visit. Cross-resistance between RPV and other NNRTIs was shown for EFV, ETR, and NVP in these three participants. The participants with treatment-emergent NRTI resistance-associated substitutions showed phenotypic resistance to 3TC and FTC.

Conclusion
A high rate of virologic failure and resistance emergence to RPV and other drugs in the regimen was seen in Study C213. Virologic failure in this population is most likely associated with nonadherence.

In Study C213 Cohort 1, a single-arm, open-label phase 2 trial in antiretroviral treatment-naïve HIV-1-infected pediatric participants ≥12 to less than 18 years, RPV resistance-associated substitutions were observed in 63% (5/8) of participants with virologic failure and post-baseline genotypic data at 48 weeks. The RPV resistance-associated substitutions detected in these five participants were E138K (n=4), K101E (n=2), M230L (n=2), E138G (n=1), E138R (n=1), Y181I (n=1), and H221Y (n=1) consistent with substitutions seen in adults failing on an RPV-containing regimen. Four of the five virologic failure participants with RPV substitutions had ≥2.5-fold decrease in susceptibility to RPV. In addition, four of the five virologic failure participants with RPV resistance substitutions also had at least one treatment-emergent resistance substitution to nucleos(t)ide reverse transcriptase inhibitors.

In Study C213 Cohort 2, a single-arm, open-label phase 2 study in antiretroviral treatment-naïve HIV-1-infected pediatric participants ≥6 to less than 12 years of age, six participants experienced virologic failure on RPV-containing regimens (6/18, 33%) (three participants failed ≤48 weeks and three participants failed after 48 weeks). Additionally, three of the virologic failures were <25 kg and three were >25 kg in weight. Of the six virologic failures, five (83%) had treatment-emergent RPV resistance-associated substitutions [K101E (n=3), E138Q or K (n=3), Y181C (n=1), H221Y (n=2), P225P/L (n=1), M230M/L (n=1)], with four also showing reduced RPV susceptibility phenotypically (2- to 115-fold). The emergent RPV resistance-associated substitutions in pediatric patients are consistent with those seen in adults failing on a RPV-containing regimen.

In addition to RPV resistance emergence, four of the virologic failures also had treatment-emergent resistance substitutions to other drugs in their antiretroviral regimen [M184V (n=3) and M184M/I (n=1) conferring decreased susceptibility to lamivudine; K65R/Y115F (n=1) conferring decreased susceptibility to abacavir, and M41L (n=1), a zidovudine resistance-associated substitution].

This information was added to Section 12.4 of the USPI.

8. Therapeutic Individualization

No new studies were conducted to support therapeutic individualization in pediatric patients receiving RPV. The effects of intrinsic and extrinsic factors on the PK of RPV have been characterized in adults.

9. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections

Clinical site inspections were not performed. According to the Applicant, all studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Council for

Harmonisation guideline for Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

10. Advisory Committee Summary

These applications were not taken to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and there were no controversial issues that would benefit from discussion by an advisory committee.

III. Appendices

11. Pharmacology Toxicology: Additional Information and Assessment

RPV is an FDA-approved drug. No additional nonclinical data were submitted.

12. Clinical Pharmacology: Additional Information and Assessment

12.1. Bioanalytical methods

Three bioanalytical methods were used in clinical studies and are considered acceptable. BA1674 is a fully validated LC-MS/MS method used for the analyses of RPV in heparin plasma samples in Study C213. BA1674 was previously reviewed for Part 1 of Study C213 (NDA202022, Supplement 8). The bioanalytical method utilized for HTX2002 (BA13223) is essentially the same as BA1674, except that the upper limit of quantification was reduced from 2000 to 500 ng/mL. The bioanalytical method (BA10241) utilized for TMC278IFD1008 was a partially validated LC-MS/MS method for quantifying RPV in ethylenediaminetetraacetic acid plasma samples. BA10241 was developed based on the validated method, BA1674, for quantification of RPV in heparin plasma samples. The only difference between these two methods was the anticoagulant used.

Table 18. Summary of Bioanalytical Method Validation and Performance

Method/Report	**Findings**	
Study C213: *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 (Cohort 2 for children aged 6 to <12 years of age)*		
Analyte/assessment	Rilpivirine: Bioanalytical method validation and performance are acceptable	
Method	BA1674: LC-MS/MS	
Matrix	Human Li-heparin plasma	
Validation reports	Validation report provided: \\CDSESUB1\EVSPROD\nda202022\0141\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ba1674\ba1674.pdf	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
Performance reports	Performance reports provided:	☒ Yes ☐ No
	Samples analyzed within the established stability period (828 days at -20°C and -70°C)	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No

	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Is an inspection for bioanalytical site be requested?	☒ Yes ☐ No
Study HX2002: *A Phase 2, Open-label, Single-arm, Multicenter Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Efficacy of Switching to RPV Plus Other ARVs in HIV-1-infected Children (Aged 2 to <12 years) who are Virologically Suppressed*		
Analyte/assessment	Rilpivirine: Bioanalytical method validation and performance are acceptable	
Method	BA13223: LC-MS/MS	
Matrix	Human Li-heparin plasma	
Validation reports	Validation (partial) report provided: \\CDSESUB1\EVSPROD\nda202022\0251\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ba13223\ba13223.pdf	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
Performance reports	Performance reports provided: \\CDSESUB1\EVSPROD\nda202022\0251\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-hiv-1-infection\5352-stud-rep-uncontr\tmc278htx2002\bss-tmc278htx2002-w24.pdf	☒ Yes ☐ No
	Samples analyzed within the established stability period (861 days at -20°C)	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Is an inspection for bioanalytical site be requested?	☒ Yes ☐ No
Study TMC278IFD1008: *A Phase 1, open-label, randomized, 2-panel, 4-way crossover study in healthy adult subjects to assess the rilpivirine relative bioavailability compared to the 25-mg oral tablet and the food effect following single dose administration of oral pediatric formulation candidates*		
Analyte/assessment	Rilpivirine: Bioanalytical method validation and performance are acceptable	
Method	BA10241: LC-MS/MS	
Matrix	Human plasma (K_2EDTA)	
Validation reports	Validation (partial) report provided: \\CDSESUB1\EVSPROD\nda202022\0251\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\ba10241\ba10241.pdf	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
Performance reports	Performance reports provided: \\CDSESUB1\EVSPROD\nda202022\0251\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\tmc278ifd1008\bqs-report-clinical-pk-tmc278ifd1008.pdf	☒ Yes ☐ No
	Samples analyzed within the established stability period (769 days at -20°C and -70°C)	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No

	Overall performance reasonable	☒ Yes ☐ No
Inspection	Is an inspection for bioanalytical site be requested?	☒ Yes ☐ No

Bioanalytical site inspection has been requested for TMC278IFD1008, C213 Cohort 2 and HTX2002. The bioanalytical sites are the same for these studies. The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed because a Remote Regulatory Assessment (RRA) for the site was conducted in February 2023 with no major concerns.

12.2. Pharmacometrics Review

The population PK model was considered appropriate for describing the observed RPV concentrations and performing PK simulations to predict steady-state RPV exposure metrics ($C_{max,ss}$, AUC_{ss}, $C_{trough,ss}$) in children. More specifically, the updated population PK model was utilized to support the current submission as outlined below:

Table 19. Utility of the Population PK Modeling

Utility of the final model		**Reviewer's Comments**
Derive PK parameters and exposure metrics for different weight bands	• A PK model developed in adults, was used to fit new RPV PK data in adolescent and children from Studies C213 and HTX2002. • Body weight was identified as the major covariate affecting RPV apparent clearance and volume of distribution. In addition, children with HIV in Study HTX2002 were estimated 43% higher bioavailability compared to adults, adolescents, and children with HIV of the other studies. • The updated PK model was used to compare RPV exposure metrics (C_{max}, AUC_{ss}, $C_{trough,ss}$) in different body weight groups, and justify the adequacy of the proposed doses in lower body weight group. • The predicted AUC_{ss} for the proposed doses (12.5 mg QD for participants with ≥10 to <20 kg, 15 mg QD for ≥20 to <25 kg, and 25 mg QD for ≥25 kg) were generally within the target exposure range of the predicted adult mean AUC_{ss}, except for the 12.5 mg dose in the 10 to 16 kg and the 25 mg dose in the 25 to 40 kg, where the predicted	• The reviewer's assessment of the updated PK model and the conducted sensitivity analyses found that the Applicant's PK model adequately describes and predicts PK in adults, adolescents, and children. • The higher bioavailability in Study HTX2002 is likely not due to differences in formulations, batch numbers, sites or cohorts of studies or other intrinsic factors (e.g., weight, disease status, etc.). • RPV exposure metrics are consistent and overlapping in participants with body weight groups 10 to 50 kg, under the proposed dosing, except for a higher median AUC_{ss}, $C_{max,ss}$ for the 10 to 15 kg and the 25 to 30 kg group. The median exposure is expected to decrease as body weight increases above 50 kg, however it remains within the observed range of exposure metrics in adults. The predicted exposure metrics are also in agreement with those estimated

	mean AUC_{ss} was higher than the target exposure. • Although these weight groups were predicted to higher mean exposure than adults, the 95th percentile of the predicted $C_{max,ss}$ was below the safety threshold (750 ng/mL) across the entire body weight range at the proposed doses.	for the different weight groups in Studies C213, HTX2002 and adult studies (C209 and C215), with body weight ranging from 16 to 104 kg. • In weight groups with higher exposure, the 95th percentile of the predicted $C_{max,ss}$ is expected to be well below or in the highest anticipated clinical exposure (per study HTX2002) around 605 ng/mL, which was the concentration associated with a QTc prolongation up to 10 ms per previous FDA review.

12.2.1. Applicant's PK Analysis

The popPK analysis used to describe the observed PK data from study C213 (treatment-naïve patients with HIV-1 ≥6 to <18 years old) and study HTX2002 (virologically suppressed children with HIV-1 ≥2 to <12 years old) was based on a previously developed structural PK model describing RPV PK in adults (Study C209 and Study C215).

Table 20 summarizes the studies included in the updated PK model and the PK sampling schedule. The final PK dataset used for updated PK analysis consisted of 1201 quantifiable PK samples from 127 participants. Concentrations below the limit of quantification (n=7) were excluded from the analysis dataset as they represented 0.6% of all the data. Table 21 summarizes the demographic characteristics of all participants stratified by study and cohort.

Table 20. Studies Included in the Population PK Analysis

Study Number	Study Title & Design	Number of Participants	Dosing Regimen	PK Assessments
TMC278-TiDP6-C209 (C209)[a] Only PK substudy data used	A Phase III, randomized, double-blind trial of TMC278 25 mg qd versus efavirenz 600 mg qd in combination with a fixed background regimen consisting of tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve HIV-1-infected subjects.	PK substudy: n=13 (actual)	25 mg RPV qd	In PK substudy, PK samples collected predose (within 15 minutes of RPV intake), and at 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose.
TMC278-TiDP6-C215 (C215)[a] Only PK substudy data used	A Phase III, randomized, double-blind trial of TMC278 25 mg qd versus efavirenz 600 mg qd in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors in antiretroviral-naïve HIV-1-infected subjects.	PK substudy: n=34 (actual)	25 mg RPV qd	In PK substudy, PK samples collected predose (within 15 minutes of RPV intake), and at 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose.
TMC278-TiDP38-C213 (C213)[a]	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.	Cohort 1 (children ≥12 to <18 years of age): n=36 (actual) Cohort 2 (children ≥6 to <12 years of age): n=18 (actual)	Children with a body weight of ≥25 kg: 25 mg RPV qd Children with a body weight of ≥20 to <25 kg: 15 mg RPV qd 5 children received 25 mg RPV before the decision to adjust the dose to 15 mg was made Children with a body weight of <20 kg: 12.5 mg RPV qd	**PK sampling (sparse)** Collected at any time in the following visits: W2, 4, 8, 12, 24, and 48. **PK sampling (intensive)** Cohort 1 Part 1a children: collected at W2 Cohort 1 Part 1b children: collected at W4 Cohort 2 children with body weight <25 kg: collected at W2 PK samples (intensive) collected predose (within 1 hour of RPV intake), and at 2, 4, 5, 6, 9, 12, and 24 hours postdose.
TMC278HTX2002 (HTX2002)	A Phase II, Open-label, Single-arm, Multicenter Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Efficacy of Switching to RPV Plus Other ARVs in HIV-1-infected Children (Aged 2 to <12 years) who are Virologically Suppressed.	n=26 (actual)	Children with a body weight of ≥25 kg: 25 mg RPV qd Children with a body weight of ≥20 to <25 kg: 15 mg RPV qd Children with a body weight of <20 kg: 12.5 mg RPV qd (1 child received 15 mg RPV before the decision to adjust the dose to 12.5 mg was made)	**PK sampling (sparse)** Collected at any time in the following visits: W2, 4, 8, 12, 24, and 48. **PK sampling (intensive), optional PK substudy** Children with body weight <25 kg: collected at W4 Children with body weight ≥25 kg: collected after at least 4 weeks, of which at least 2 weeks on the 25 mg qd dose. PK samples (intensive) collected predose (within 1 hour of RPV intake), and at 2, 4, 5, 6, 9, 12, and 24 hours postdose.

ARV=antiretroviral; HIV=human immunodeficiency virus; n=number of participants; PK=pharmacokinetic; popPK=population PK; qd=once daily; RPV=rilpivirine; W=week.

[a] Study was used for previous popPK model development (Population PK Analysis 2015; Appendix 1).

Source: Applicant's Population PK Report, Table 1, pages 17 and 18.

Table 21. Summary of Demographic Characteristics, Stratified by Study

	C209	C215	C213 Cohort 1	C213 Cohort 2			HTX2002		
	25 mg (N=13)	25 mg (N=34)	25 mg (N=36)	12.5 mg (N=2)	15 mg (N=2)	25 mg (N=14)	12.5 mg (N=2)	15 mg (N=6)	25 mg (N=18)
Age (years)									
Mean (SD)	37.3 (11.4)	39.5 (8.31)	14.5 (1.70)	6.00 (0)	6.50 (0.707)	9.36 (1.39)	6.80 (1.27)	8.22 (1.73)	10.3 (1.35)
Median [Min, Max]	36.0 [22.0, 59.0]	38.0 [23.0, 59.0]	14.5 [12.0, 17.0]	6.00 [6.00, 6.00]	6.50 [6.00, 7.00]	10.0 [7.00, 11.0]	6.80 [5.90, 7.70]	7.95 [6.20, 11.0]	10.6 [6.90, 11.9]
Baseline weight (Kg)									
Mean (SD)	68.6 (15.9)	71.8 (9.47)	46.3 (10.5)	17.0 (0)	23.5 (1.06)	28.6 (7.40)	16.9 (0.919)	22.7 (1.83)	34.9 (8.69)
Median [Min, Max]	67.0 [43.0, 104]	71.6 [56.0, 102]	45.2 [32.8, 93.2]	17.0 [17.0, 17.0]	23.5 [22.7, 24.2]	26.3 [22.6, 51.4]	16.9 [16.2, 17.5]	23.2 [19.3, 24.6]	35.4 [25.2, 60.0]
Baseline BMI (kg/m2)									
Mean (SD)	23.3 (4.05)	23.4 (2.98)	19.6 (3.74)	14.7 (0.141)	15.3 (1.06)	16.2 (2.37)	13.6 (1.06)	14.6 (0.874)	18.1 (3.07)
Median [Min, Max]	23.7 [17.2, 29.9]	23.3 [18.7, 30.2]	18.9 [14.9, 35.8]	14.7 [14.6, 14.8]	15.3 [14.5, 16.0]	15.9 [13.6, 22.8]	13.6 [12.8, 14.3]	14.8 [13.3, 15.8]	17.4 [14.6, 25.3]
Sex									
Male	9 (69.2%)	31 (91.2%)	16 (44.4%)	1 (50.0%)	1 (50.0%)	9 (64.3%)	1 (50.0%)	3 (50.0%)	12 (66.7%)
Female	4 (30.8%)	3 (8.8%)	20 (55.6%)	1 (50.0%)	1 (50.0%)	5 (35.7%)	1 (50.0%)	3 (50.0%)	6 (33.3%)
Race									
White	7 (53.8%)	24 (70.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50.0%)	0 (0%)	5 (27.8%)
Asian	4 (30.8%)	3 (8.8%)	4 (11.1%)	0 (0%)	0 (0%)	2 (14.3%)	1 (50.0%)	1 (16.7%)	5 (27.8%)
Black or African American	2 (15.4%)	7 (20.6%)	32 (88.9%)	2 (100%)	2 (100%)	12 (85.7%)	0 (0%)	5 (83.3%)	8 (44.4%)
Hepatitis B									
Negative	11 (84.6%)	32 (94.1%)	33 (91.7%)	2 (100%)	1 (50.0%)	14 (100%)	2 (100%)	6 (100%)	17 (94.4%)
Positive	1 (7.7%)	2 (5.9%)	3 (8.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	1 (50.0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.6%)
Hepatitis C									
Negative	12 (92.3%)	32 (94.1%)	36 (100%)	2 (100%)	1 (50.0%)	14 (100%)	2 (100%)	6 (100%)	17 (94.4%)
Positive	0 (0%)	2 (5.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	1 (50.0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.6%)
PK sampling									
Sparse	0 (0%)	0 (0%)	13 (36.1%)	0 (0%)	0 (0%)	4 (28.6%)	0 (0%)	0 (0%)	17 (94.4%)
Intensive	13 (100%)	34 (100%)	23 (63.9%)	2 (100%)	2 (100%)	10 (71.4%)	2 (100%)	6 (100%)	1 (5.6%)
Formulation									
25 mg tablet	13 (100%)	34 (100%)	36 (100%)	0 (0%)	0 (0%)	14 (100%)	0 (0%)	0 (0%)	18 (100%)
2.5 mg tablet	0 (0%)	0 (0%)	0 (0%)	2 (100%)	2 (100%)	0 (0%)	2 (100%)	6 (100%)	0 (0%)

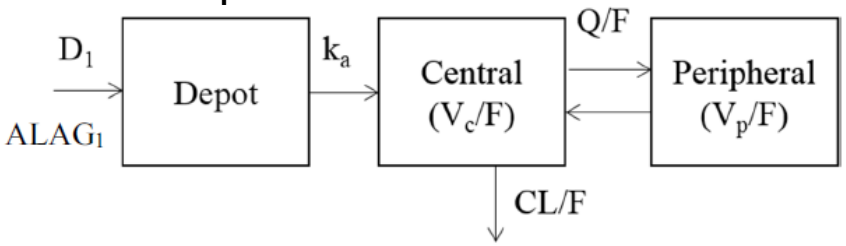
Note: the summary of demographic characteristics is based on the PK dataset used for PK modelling.

Source: FDA Reviewer.

Final Population PK model

The parameter estimates from the updated final PK model describing RPV PK are listed in Table 22. The structural PK model was similar to the previously developed PK model and consisted of a 2-compartment disposition model with a zero-order input of the drug into the depot compartment (gut) and a delayed first-order absorption (lag-time) into the central compartment. A schematic of the structural PK model of RPV is represented in Figure 3.

Figure 3. Schematic of the Population PK Model



$ALAG_1$=lag time; CL/F=apparent clearance; D_1=zero-order duration; k_a=first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent intercompartmental clearance; V_c/F=apparent volume of distribution of the central compartment; V_p/F=apparent volume of distribution of the peripheral compartment.

Source: Applicant's Population PK Report, Figure 1, page 21.

Body weight (standardized to 70 kg) was included as a covariate on apparent clearance (CL/F), the apparent central volume of distribution (Vc/F) and the apparent intercompartment CL (Q/F), using allometric scaling with power exponents fixed to 0.75 for CL/F and 1 for Vc/F. Participants in study HTX2002 were estimated to have a 43% higher bioavailability (F1) compared to participants in studies C123, C209, and C215.

Inter-individual variability (IIV) was included on CL/F, Q/F and Vc/F. The residual error model consisted of an additive error on log-transformed RPV concentrations.

The goodness of fit (GOF) plots from the final PK model are shown in Figure 4 and the prediction-corrected visual predict check (pcVPC) stratified by study are shown in Figure 5.

Table 22. Parameter Estimates from the Final PK Model

Parameter	Estimate (RSE%)
CL/F, L/h	14.8 (4.6)
V_c/F, L	818 (12.8)
Q/F, L/h	12.4 (68.0)
V_p/F, L	70.2 (41.7)
k_a, h^{-1}	3.06 (30.3)
$ALAG_1$, h	1.18 (13.6)
F1	1 FIX
D_1, h	2.23 (17.7)
Allometric scaling exponent on CL/F and Q/F	0.75 FIX
Allometric scaling exponent on V_c/F	1 FIX
Study HTX2002 on F1	1.43 (8.4)
IIV on CL/F[a]	0.174 (11.9) (CV=41.8%) (shr=4.0%)
IIV on V_c/F[a]	0.729 (28.8) (CV=85.4%) (shr=25.3%)
Correlation between IIVs on CL/F and V_c/F[b]	0.552 (15.5)
RUV	0.0995 (10.3) (CV=31.5%)
Objective function value	-1,126.096

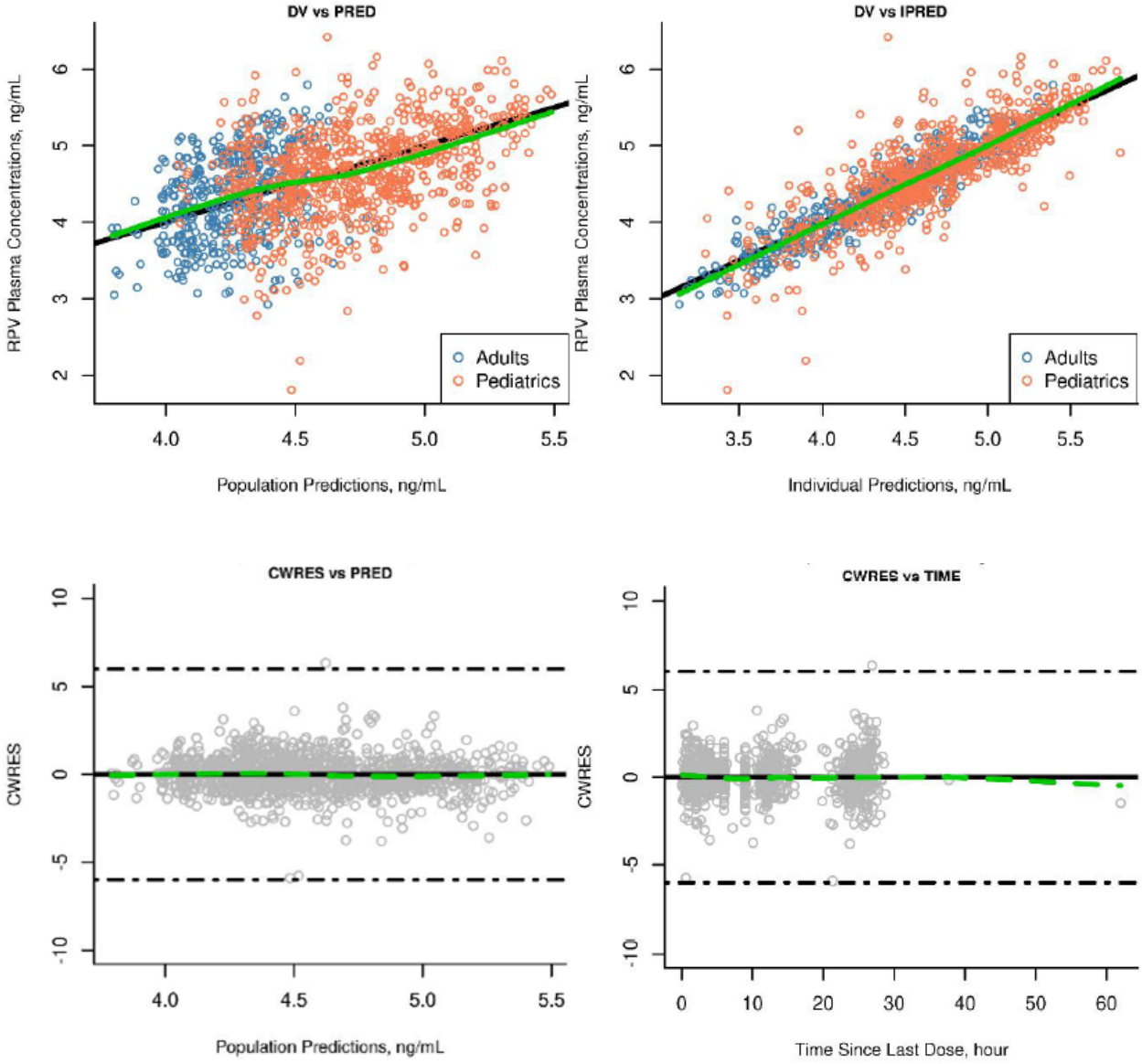
$ALAG_1$=lag time; CL/F=apparent clearance; CV=coefficient of variation; D_1=zero-order duration; F1=apparent bioavailability; FIX=fixed; HTX2002=TMC278HTX2002; IIV=interindividual variability; k_a=first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent intercompartmental clearance; RSE=relative standard error; RUV=residual unexplained variability; shr=shrinkage; V_c/F=apparent volume of distribution of the central compartment; V_p/F=apparent volume of distribution of the peripheral compartment.

[a] OMEGA value and the RSE of the OMEGA.

[b] Correlation coefficient obtained from the estimated parameters of the OMEGA block and the RSE of the correlation coefficient.

Source: Adapted from Applicant's Population PK Report, Table 4, page 26.

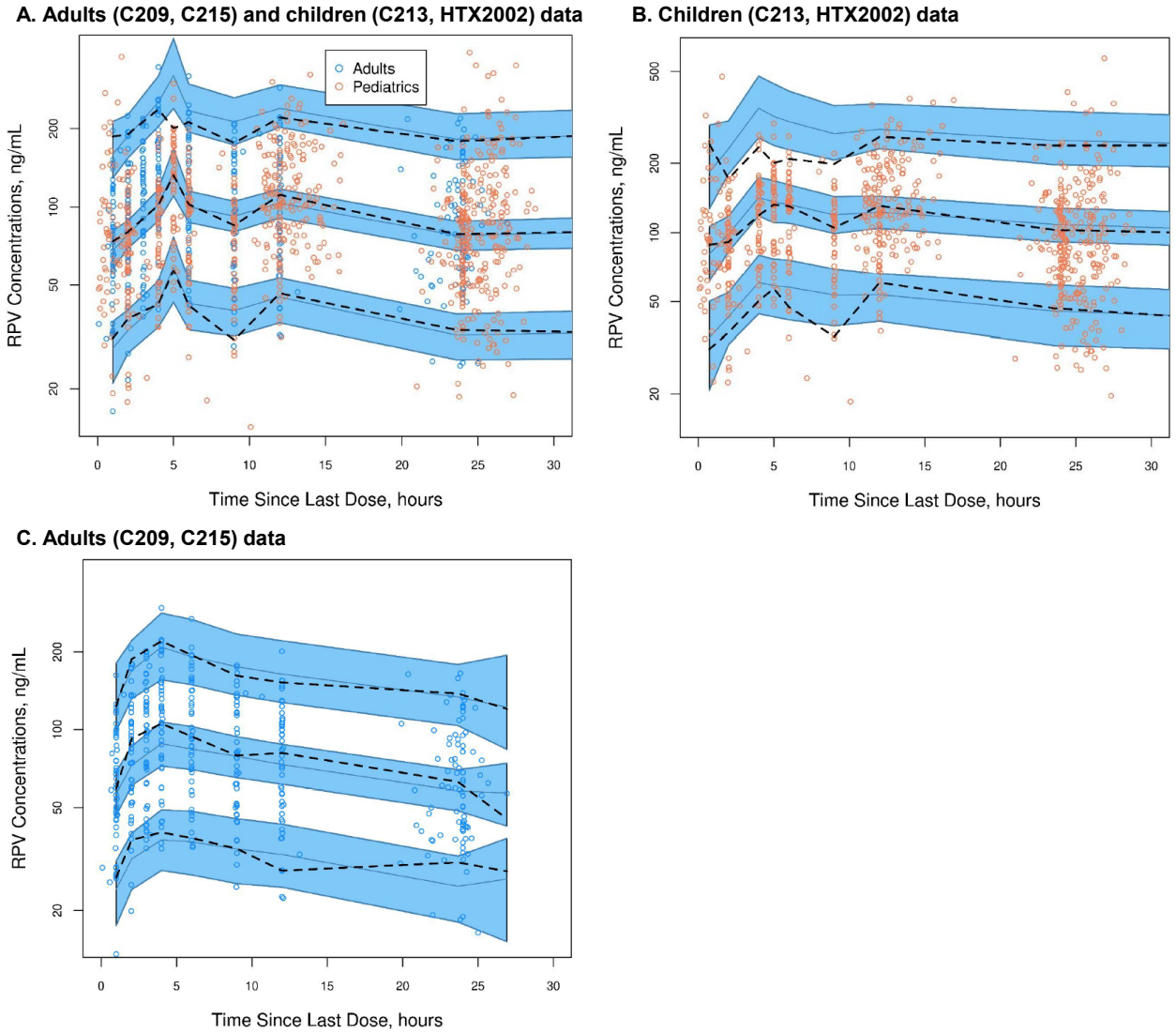
Figure 4. Goodness of Fit Plots from the Final PK Model, Stratified by Age Groups



Note: CWRES=conditional weighted residuals; DV=observations (log-transformed concentrations); IPRED=individual predictions; PRED=population predictions. Orange or blue dots represent individual concentrations in participants younger than 18 years old or 18 years old and older, respectively. Green solid or dashed lines represent loess smooth curves, and the black solid lines represent the line of unity (y = x) or y = 0.

Source: Applicant's Population PK Report, Appendix 12, page 157.

Figure 5. Prediction-corrected Visual Predictive Check from Final PK Model



Note: Graphs are on a semi-log scale. Visual predictive checks were based on simulations from 1,000 replicates of the analysis dataset. Open symbols: observed RPV concentrations (blue: adults, orange: adolescents and children). Black dashed lines: 5th, 50th, and 95th percentiles of the observed concentrations; blue ribbons: 95% confidence intervals of the 5th, 50th, and 95th percentiles of the predicted concentrations.

Source: Applicant's Population PK Report, Appendices 19 a-c, pages 176-178.

Reviewer's Comments and Assessment of the Population PK model:

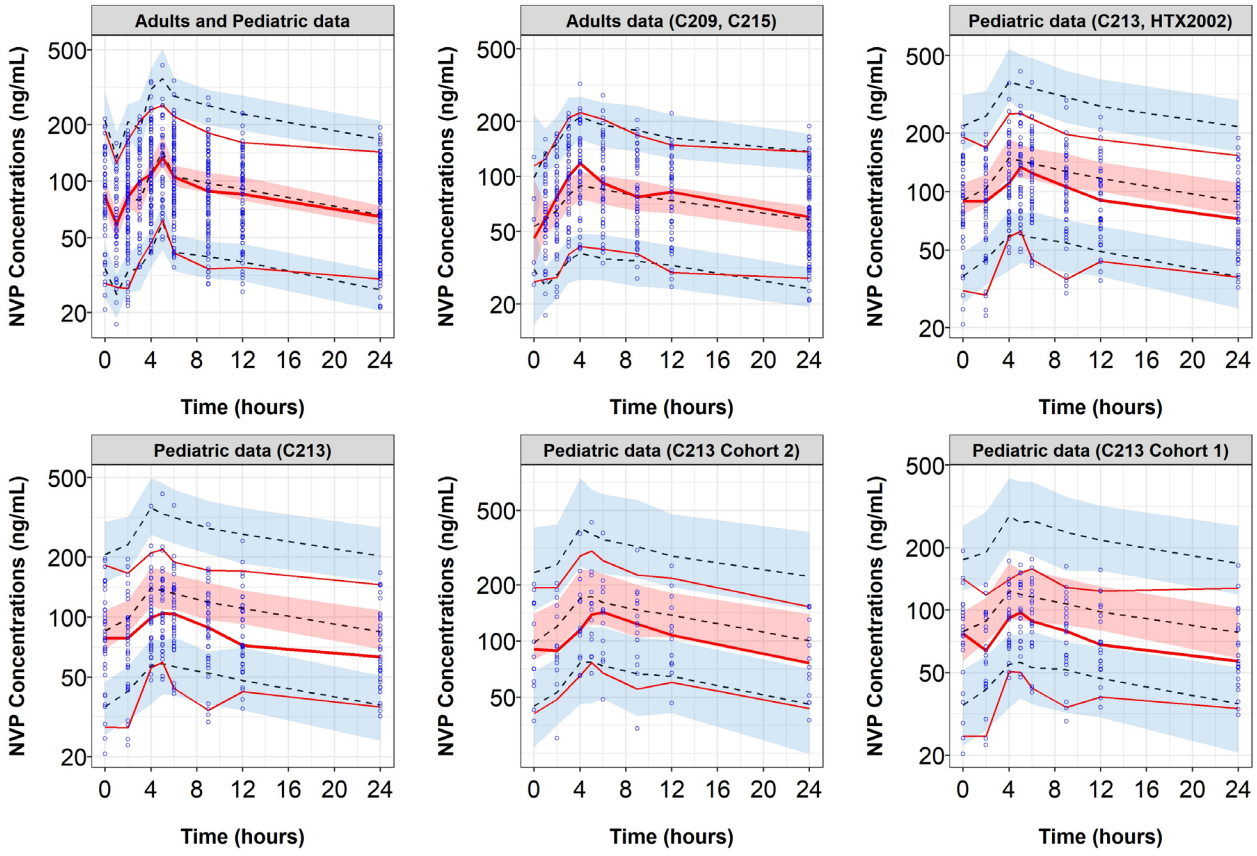
- The interindividual random error (eta-) shrinkage on PK parameters (CL/F and Vc/F) were not larger than 25% and acceptable for the reliable assessment of covariate effects on CL, V_c. The residual error (epsilon-) shrinkage was low (< 10%), indicating the informativeness of the goodness of fit (GOF) plots to diagnose structural and residual error model misspecifications.

- The GOF plots stratified by age indicate that the Applicant's PK model captures and describes the observed RPV concentrations in pediatrics and adults. The reviewer's

assessment of the GOF plots stratified by study showed that the PK model reasonably describes the observed RPV concentrations in each study.

The pcVPCs either from all studies together or stratified by study population (pediatrics and adults) also show that the PK model appropriately captures the median PK profiles and the PK variability of RPV concentrations over-time, including peak (Cmax) and trough concentrations. For the pediatric Study C213 (Cohort 1 and 2), the pcVPC shows that the model tends to slightly overpredict the median PK profiles (Figure 6Figure 6). In Figure 4, the pcVPC from intensive PK data of Study HTX2002 is showing overlapping 95% CI, likely due to fewer patients with rich PK sampling.

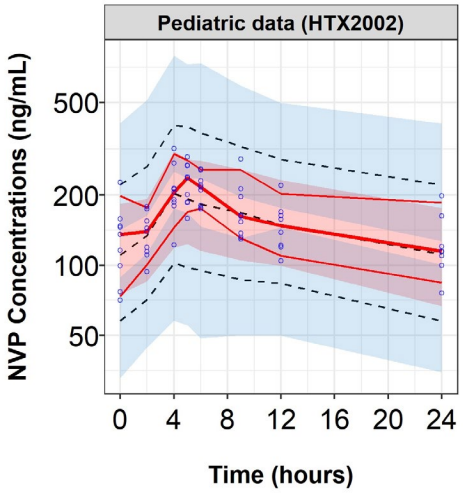
Figure 6. Prediction-corrected Visual Predictive Checks of Intensive PK Sampling Data, Stratified by Study and Study Population



Note: Graphs are on a semi-log scale. Visual predictive checks were based on simulations from 200 replicates of the analysis dataset. Open symbols: observed RPV concentrations. Red solid lines: 5th, 50th, and 95th percentiles of the observed concentrations from intensive PK sampling; Black dashed red lines: 5th, 50th, and 95th percentiles of the simulated concentrations; Shaded areas: 95% confidence intervals of the 5th, 50th, and 95th percentiles of the predicted concentrations.

Source: FDA reviewer.

(Figure 6 *continued*)



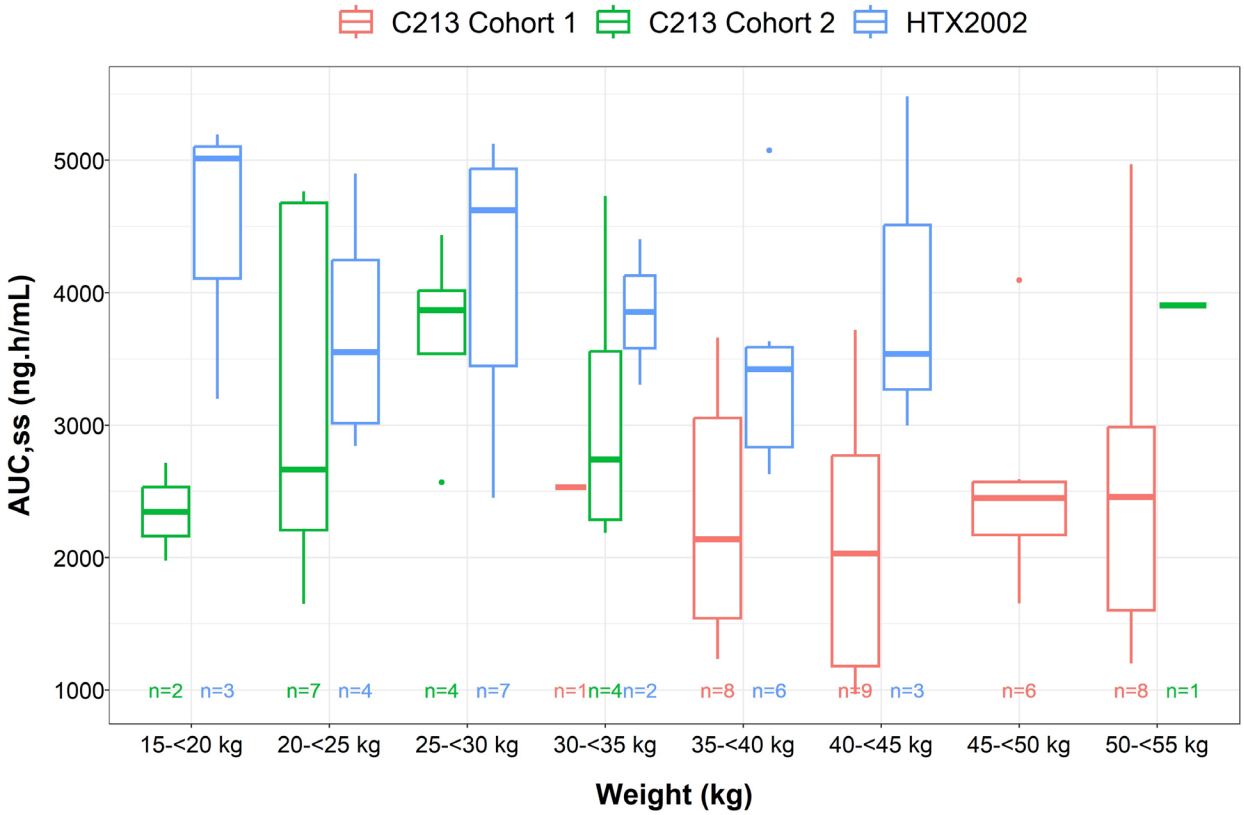
Note: Graphs are on a semi-log scale. Visual predictive checks were based on simulations from 200 replicates of the analysis dataset. Open symbols: observed RPV concentrations. Red solid lines: 5th, 50th, and 95th percentiles of the observed concentrations from intensive PK sampling; Black dashed red lines: 5th, 50th, and 95th percentiles of the simulated concentrations; Shaded areas: 95% confidence intervals of the 5th, 50th, and 95th percentiles of the predicted concentrations.
Source: FDA reviewer.

- Participants in Study HTX2002 were estimated to have a 43% higher bioavailability (F1) compared to participants in Studies C123 (Cohort 1 and 2), C209 and C215. The reason for the higher bioavailability and therefore higher exposure observed in Study HTX2002 was not identified and could not be imputed with certainty to the change in the bioanalytical method. The higher exposure was not found to be associated to formulations (tablet vs. tablet for oral suspension), formulation batch numbers, sites or cohorts of studies or other intrinsic factors (e.g., age, disease status, etc.).

  Covariate plots from the base model (adjusting for body weight) showed that study HTX2002 showed consistently higher exposure (represented by lower CL/F and Vc/F) compared to study C213 Cohort 2 for the same formulation, formulation batch number and study site. Information on food intake in Studies C213 and HTX2002 was not available.

  The difference in median body weight between pediatric participants receiving RPV 25 mg in Study HTX2002 (mean weight=35.4 kg) and Study C213 Cohort 2 (mean weight=26.3) could not explain the difference in exposure as the PK model adjusted the effect of body weight on CL/F and Vc/F. Figure 7 shows the distribution of the model-predicted AUCss (from the base model) by weight group and study. Study HTX2002 showed consistently higher AUCss compared to Study C213 for the same weight group, suggesting that body weight differences between studies do not explain the difference in exposure.

Figure 7. Predicted RPV AUC_{ss}, Stratified by Weight and Study



Note: model predicted steady-state AUC based on individual PK parameters estimated form the base model, with only body weight as covariate.
Source: FDA reviewer

A relative bioavailability comparability study (Study TMC278IFD1008) identified that the bioavailability of RPV as 10×2.5 mg tablets for oral suspension was 33% higher than the marketed 25 mg tablet, when administered after a standard breakfast. The FDA's reviewer used the PK model to estimate the differences in bioavailability between formulation (2.5 mg tablets for oral suspension and 25 mg tablet). The PK model was not able to estimate a difference in bioavailability between the 2.5 mg tablets for oral suspension and the 25 mg tablet in Study C213 but estimated a higher F1 of 54% and 38% in study HTX2002 in patients who received the tablets for oral suspension and the 25 mg tablet, respectively. However, this difference between formulations in Study HTX2002 was not statistically significant, as the objective function value (OFV) of the model (with 1 additional degree of freedom) was similar to the original model.

An alternative PK covariate model where the bioavailability of the 2.5 mg tablets for oral suspension was fixed to 30% (per the PK comparability study results) for study C213 estimated a higher F1 of 26% in participants who received the 2.5 mg tablets for oral suspension in Study HTX2002 and a higher F1 of 39.5% in participants who received the 25 mg tablet in Study HTX2002. The OFV of the model increased compared to the original fit indicating no improvement in the model fit.

In conclusion, the reviewer's sensitivity analyses suggest that the higher bioavailability of 43% estimated by the Applicant in Study HTX2002 is likely not due to differences in formulations, formulations batch numbers, sites or cohorts of studies or other intrinsic factors (e.g., age, disease status, etc.), but likely inherent to Study HTX2002, in which patient had higher exposure compared to Study C213 Cohort 2, Study C213 Cohort 1, Study C215 and Study C209.

12.2.2. Applicant's PK simulations

The pediatric studies (Study C213 Cohort 2 and Study HTX2002) did not enroll patients with a body weight lower than 16 kg and younger than 6 years old. To support the proposed use of RPV in pediatric patients weighing at least 10 kg and older than 2 years old, the Applicant performed PK simulations to predict the effect of body weight on RPV exposure metrics (AUC_{ss} and $C_{max,ss}$) and compare RPV exposure metrics between pediatric patients (with a body weight down to 10 kg) and adults.

The PK simulations were performed across body weights ranging from 10 to 70 kg, in 0.2 kg increments. Since no potential covariate could be linked to the difference in exposure between studies C213 and HTX2002, half of the simulated population was assumed to have a 43% higher bioavailability compared to the other half, which represents a 1:1 ratio for the PK simulations.

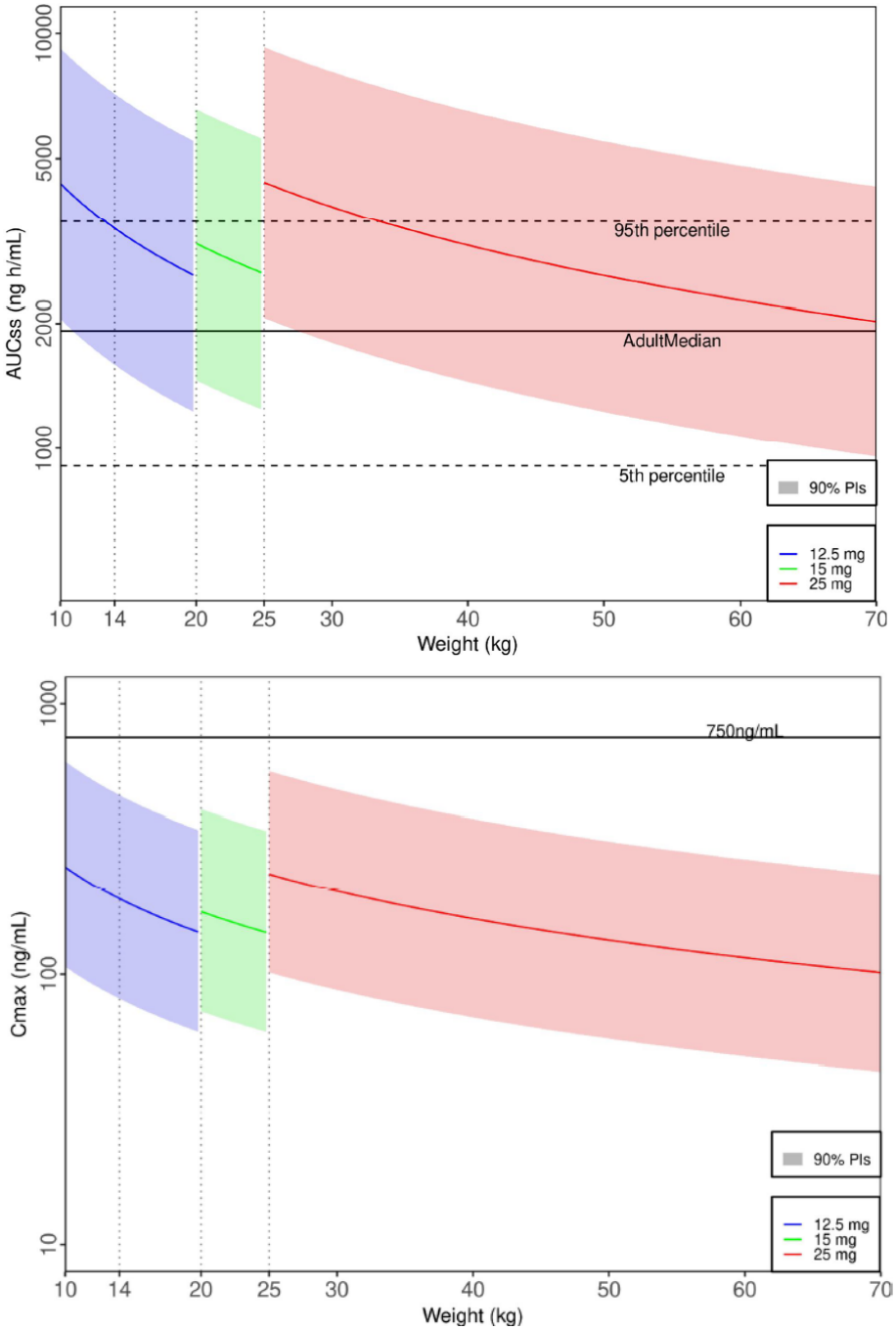
Figure 8 shows the predicted distribution of AUC_{ss} and $C_{max,ss}$ in the proposed dose setting:

- 12.5 mg QD (5×2.5 mg tablets for oral suspension) for participants weighing ≥10 to <20 kg,
- 15 mg (5×2.5 mg tablets for oral suspension) for participants with body weight ≥20 to <25 kg,
- 25 mg QD (1×25 mg tablet) for participants with body weight ≥25 kg.

The predicted distribution of AUC_{ss} appears to be higher than the predicted exposure in adults (Study C209 and C215), particularly for the weight bands of 10 to 16 kg and 25 to 40 kg.

The predicted 90% PI of $C_{max,ss}$ was below the safety threshold for QTc prolongation, as determined by the Applicant, of 750 ng/mL across the entire body weight range at the proposed doses.

Figure 8. Predicted Distribution of RPV AUC_{ss} and C_{max} in Pediatric Patients Compared to Adults



Note: Graphs are on a semi-log scale. AUC_{ss}=area under the plasma concentration-time curve at steady state. C_{max}=maximum plasma concentration at steady state. PI=prediction interval. Shaded colored area and colored solid line are the 90% PI and the geometric mean AUC_{ss} or C_{max} for each regimen. Solid black line is the adult median AUC_{ss} or C_{max}, and the dashed black lines represent the 5th and 95th percentile (90% PIs) of adult AUC_{ss} (based on pooled data of Studies C209 and C215). The value of 750 ng/mL (solid black line) represents a safety threshold for C_{max}, which was obtained through modeling and simulation of data from the thorough-QT Studies TMC278-C152 and TMC278-C131.

Source: Applicant's Population PK Report, Appendix 23 and Figure 4, pages 32 and 192.

Reviewer's Assessment of PK Simulations

- The predicted higher AUC_{ss} in pediatric participants compared to adults from the Applicant's PK simulations is likely driven by setting a 43% higher bioavailability in half of the simulated population, although the higher bioavailability was observed only from the recent Study HTX2002 (which used a different bioanalytical method). Participants in previous pediatric study (Study C213 Cohort 2) were estimated to have comparable bioavailability as adolescents (Study C213 Cohort 1) and adults (Studies C209 and C215).
- The reviewer's independent PK simulations was performed to account for two different scenarios:
    - 1st scenario: PK simulations with the reference bioavailability and typical apparent PK parameters estimated from pediatric Study C213 (cohort 1 and cohort 2) and adult studies (Studies C209 and C215).
    - 2nd scenario: PK simulations with a 43% higher bioavailability, as estimated for the pediatric Study HTX2002.

  PK simulations were performed using a pediatric population derived from the CDC growth chart (2 to 17 years old, body weight: 10 to 97 kg).

  Figure 9 shows RPV exposure metrics (AUC_{ss}, $C_{max,ss}$, and $C_{trough,ss}$) are consistent and overlapping in participants with body weight groups ranging from 10 to 50 kg, under the proposed dosing regimen and for both bioavailability scenarios, except for a higher median AUC_{ss}, $C_{max,ss}$ for the 10 to 15 kg group and the 25 to 30 kg group. The median exposure is expected to decrease as body weight increases above 50 kg, however it remains within the observed range of exposure metrics in adults.

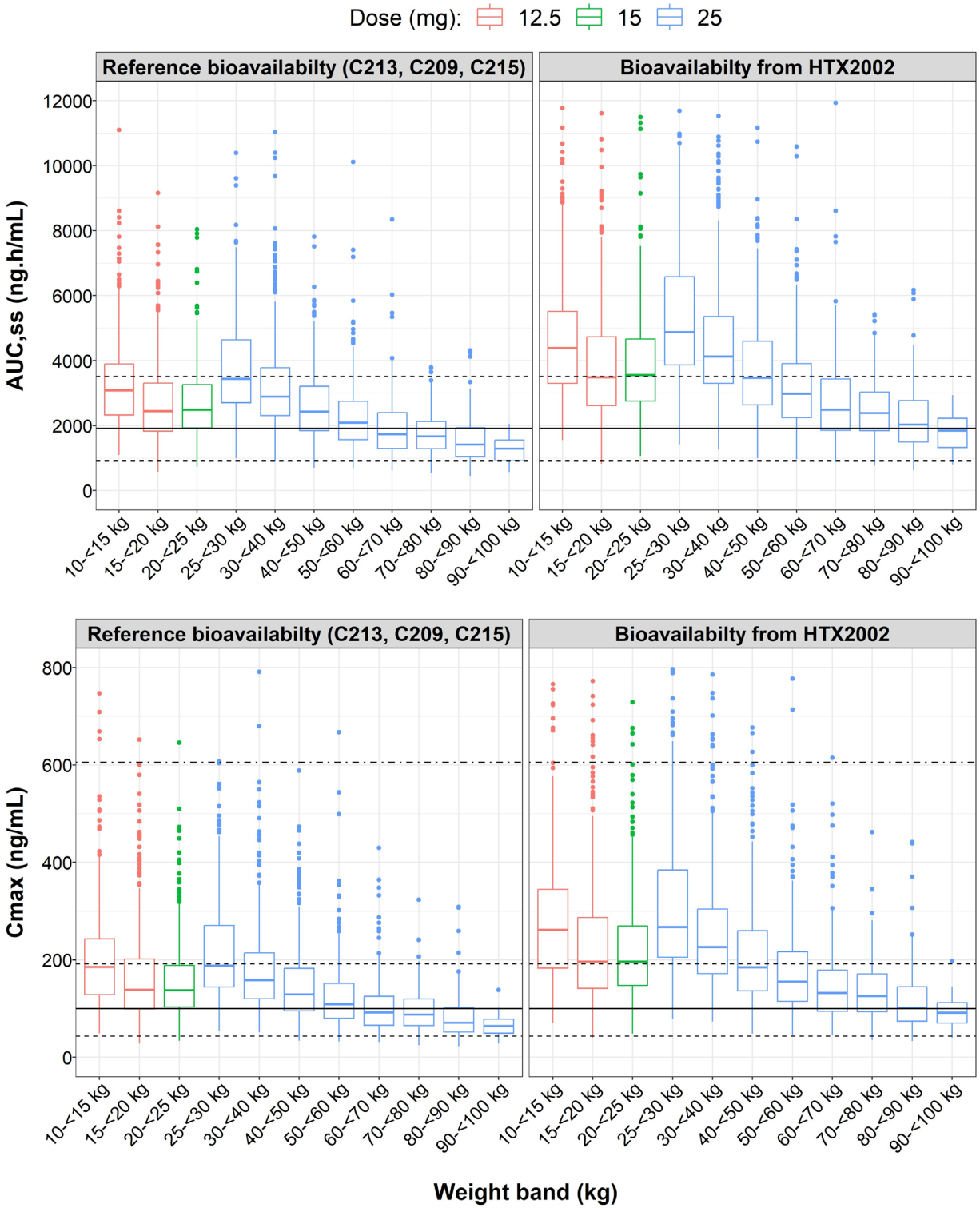
  The predicted RPV exposure metrics (AUC_{ss}, $C_{max,ss}$, and $C_{trough,ss}$) are also in agreement with those estimated for the different weight groups in study C213 (Cohort 1 and Cohort 2), study HTX2002 and adult studies (Studies C209 and C215), with body weight ranging from 16 to 104 kg (Table 21).

  In the body weight groups (10 to 15 kg and 25 to 30 kg) with a predicted higher exposure, the 95th percentile of the predicted $C_{max,ss}$ under the simulated reference bioavailability scenario (Figure 9, Table 23) is well below 605 ng/mL, which was the concentration associated with a QTc prolongation up 10 ms according to the previous thorough QT (TQT) analyses (original NDA 202022).

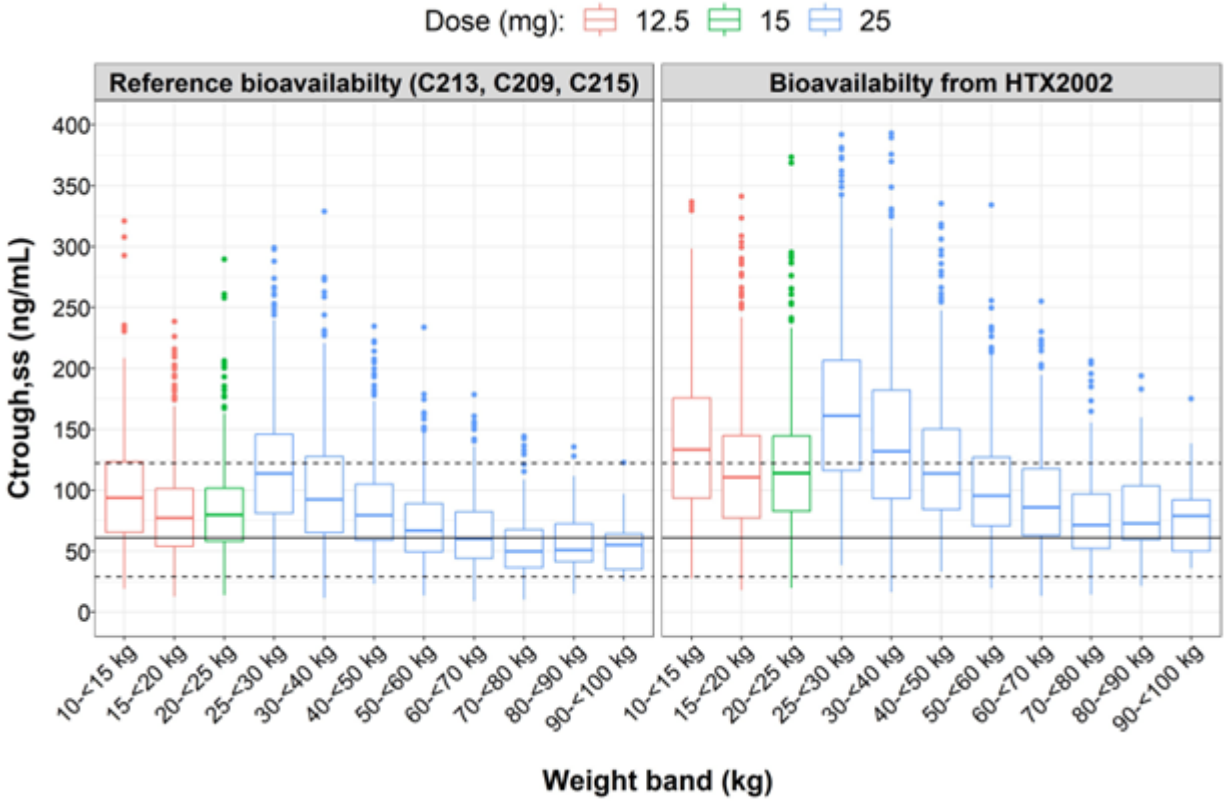
  Under the higher bioavailability of 43% as estimated from study HTX2002, the 95th percentile of the predicted $C_{max,ss}$ in the body weight groups 10 to 15 kg and 25 to 30 kg was about 607 ng/mL and 628 ng/mL, respectively, and within the range of 605 ng/mL (Table 23).

  Based on both PK simulation scenarios, the proposed dosing regimen seems acceptable and safe regarding the potential for QTc prolongation.

Figure 9. Predicted RPV AUC_{ss} and C_{max} by Weight Group, Stratified by Estimated Bioavailability



(Figure 9 *continued*)



Note: The solid and dotted lines are the overall median and 90% prediction interval predicted from studies in adults (C209 and C215, range of weight= 43 to 102 kg). The dot-dashed line at the Cmax of 605 ng/mL is the concentration associated with 10 milliseconds increase in QTC in previous TQT studies.

Source: FDA reviewer.

Table 23. Predicted Exposure Metrics by Weight Group, Stratified by Estimated Bioavailability

Weight bands (kg)	Dose (mg)	AUC_{ss} (ng.h/ml) Median (90% range)		$C_{max,ss}$ (ng/mL) Median (90% range)		$C_{trough,ss}$ (ng/mL) Median (90% range)	
		Reference Bioavailability	***Bioavailability from HTX2002***	***Reference Bioavailability***	***Bioavailability from HTX2002***	***Reference Bioavailability***	***Bioavailability from HTX2002***
10-<15	**12.5**	3054 (1535 - 6095)	4367 (2195 - 8716)	181 (82 - 424)	259 (117 - 607)	93 (42 - 194)	134 (60 - 277)
15-<20	**12.5**	2452 (1229 - 4858)	3506 (1758 - 6947)	139 (64 - 329)	199 (92 - 470)	76 (35 - 157)	108 (50 - 225)
20-<25	**15**	2442 (1229 - 4854)	3492 (1758 - 6941)	137 (64 - 311)	195 (91 - 444)	77 (35 - 159)	110 (50 - 227)
25-<30	**25**	3513 (1758 - 6970)	5024 (2514 - 9966)	194 (91 - 439)	277 (130 - 628)	111 (50 - 235)	159 (72 - 336)
30-95	**25**	2204 (1003 - 4792)	3151 (1434 - 6853)	118 (51 - 286)	168 (72 - 410)	72 (31 - 161)	103 (44 - 230)

Note: 90% range: calculated of 5th and 95th percentile of the exposure metric in each weight group of the simulated population. Reference bioavailability: based on study C213, C209, and C215. Bioavailability fromHTX2002: estimated from study HTX2002 with 43% higher bioavailability compared to the other pediatric and adult studies based on the PK model.

Source: FDA reviewer.

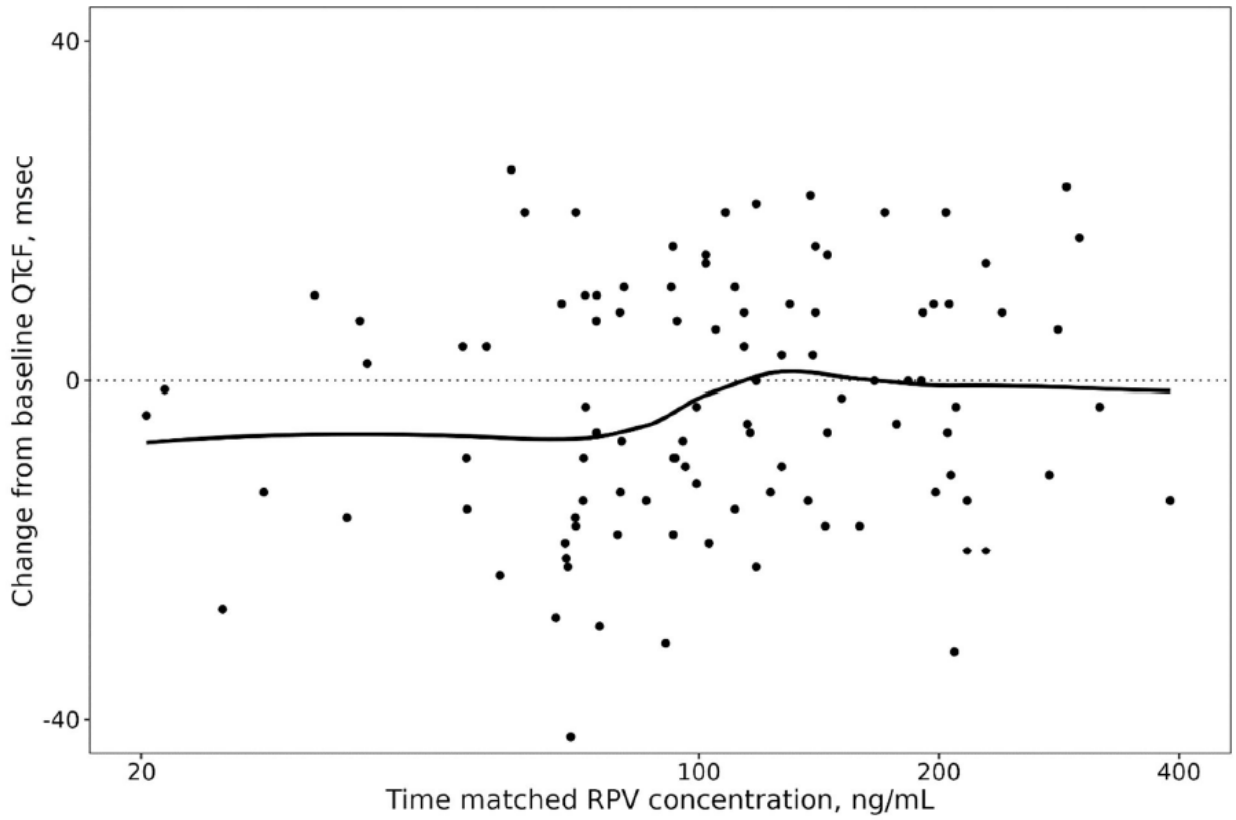
12.2.3. Applicant's QT evaluation

The exposure-response relationship for time-matched RPV plasma concentration and delta-QTcF was graphically explored for adolescents and children in Studies C213 and HTX2002. The dataset included the 572 observed delta-QTcF data from Studies C213 and HTX2002. ECG recordings were single ECGs and not taken in triplicate. The baseline QTcF in Study C213 was recorded as the screening value (i.e., no value available at baseline visit).

Of these data, only 31% of PK/ECG data pairs were within a 15-minute window that was considered acceptable for PK/ECG time-matching (i.e., 103 pairs with time difference ≤15 minutes versus 337 total pairs with time difference including >15 minutes).

Only the time-matched plasma RPV concentration and delta-QTcF pairs within a 15-minute window for participants in Studies C213 and HTX2002 were used for the exploratory concentration-QTcF analysis (Figure 10). Figure 10 did not identify a trend between the time-matched RPV concentration up to 400 ng/mL.

Figure 10. Time-matched Observed Concentration and Delta-QTcF from Studies C213 and HTX2002



C213=TMC278-TiDP38-C213; HTX2002=TMC278HTX2002; QTcF=Fridericia corrected QT; RPV=rilpivirine.
Black line indicates the locally weighted scatter plot smooth; black dotted line represents the 0-line.
Reviewer's note: the x-axis is on a log-scale.

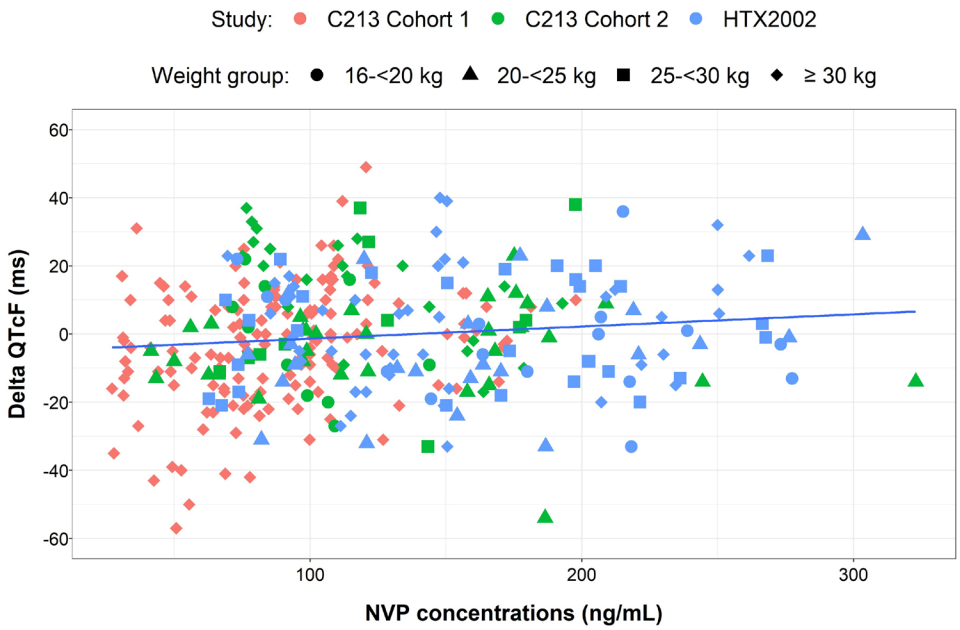
Source: Applicant's Population PK Report, Figure 5, page 33.

Reviewer's Assessment of PK Simulations

The reviewer's graphical assessment of the relationship between the model-predicted RPV concentrations at the time of QT measurement, with 335 time-matched PK model-predicted concentration and delta-QTcF pairs from Studies C213 and HTX2002. Baseline QTc ranged Baseline QTcF ranged from 355 to 450 ms, QTcF values ranged from 451 to 450 ms.

Figure 11 did not show a meaningful trend between the model-predicted RPV concentrations and QTcF measured at the same time.

Figure 11. Time-Matched Predicted Concentration and Delta-QTcF from Studies C213 and HTX2002



Source: FDA reviewer.

12.3. Individual Study Review: Study TMC278IFD1008

Study TMC278IFD1008 was a phase 1, open-label, randomized, 2-panel, 4-way crossover study in healthy adult participants. Panel 1 evaluated RPV rBA following administration of a single dose of two different oral dispersible tablet formulation candidates and of an oral granule formulation with that following administration of a single dose of the 25 mg marketed oral tablet, after a standardized breakfast (containing approximately: fat: 21 g, carbohydrates: 67 g, proteins: 19 g; calories: 533 kcal) in healthy adult participants. Each subject received 4 treatments (Treatments A, B, C, and D), randomized according to a classical 4-sequence, 4-period Williams design with a washout period of at least 14 days between treatments. Although the rBA was also evaluated for another 2 formulations, this review only focuses on the proposed formulation (G009-01, Treatment C).

- Treatment A: 25 mg RPV formulated as the 25 mg oral tablet (Edurant); fed (standardized breakfast), referred to as reference;
- Treatment B: 25 mg RPV formulated as dispersible tablet formulation G007 (10x2.5 mg tablets, dispersed in water); fed (standardized breakfast);
- Treatment C: 25 mg RPV formulated as dispersible tablet formulation G009-01 (10x2.5 mg tablets, dispersed in water); fed (standardized breakfast);
- Treatment D: 25 mg RPV formulated as granules formulation G002 (10 g of 2.5 mg/g granules, dispersed in water); fed (standardized breakfast)

In Panel 2 of Study TMC278IFD1008**,** the effect of different food (standard breakfast, fasted, or yoghurt) and dispersion (water or orange juice) conditions on the rate and extent of absorption of

the 2.5 mg tablets was assessed at a dose of 25 mg in healthy adults. Each subject received 4 treatments (Treatments E, F, G, H, as show below), randomized according to a classical 4-sequence, 4-period Williams design with a washout period of at least 14 days between treatments.

- Treatment E: 25 mg RPV formulated as dispersible tablet formulation G009-01 (10x2.5 mg tablets, dispersed in water); fed (standardized breakfast)
- Treatment F: 25 mg RPV formulated as dispersible tablet formulation G009-01 (10x2.5 mg tablets, dispersed in water); fasted
- Treatment G: 25 mg RPV formulated as dispersible tablet formulation G009-01 (10x2.5mg tablets, dispersed in orange juice [Tropicana]); fed (standardized breakfast)
- Treatment H: 25 mg RPV formulated as dispersible tablet formulation G009-01 (10x2.5 mg tablets, dispersed in water); fed (yoghurt)

PK samples were collected before RPV administration and up to 168 hours post dosing.

Reviewer Comments: The terminal half-life of RPV is approximately 50 hours. With 168 hours post dosing, there were 7 participants in the reference arm and 4 participants in the test arm whose terminal half-life and consequently AUC_∞ could not be determined accurately and/or extrapolated AUC_∞ exceeded the 20% limit.

Results: All results are available in Section II.6.4.2.

13. Summary of Study Protocols

13.1. Study C213

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

Study Design

This was a phase 2, open-label, single-arm, multicenter study to evaluate the PK, safety, tolerability, and efficacy (antiviral activity) of RPV in combination with an investigator-selected background regimen containing two N(t)RTIs in ARV treatment-naïve adolescents and children aged ≥6 to <18 years. There were two age cohorts: adolescents ≥12 to <18 years of age (Cohort 1, results reported previously) and children ≥6 to <12 years of age (Cohort 2, summarized here).

In Cohort 2 of Study C213, ARV treatment-naïve participants with HIV-1 infection aged ≥6 to <12 years with a plasma HIV-1 RNA ≥500 copies/mL but ≤100,000 copies/mL were included. After the analysis of the first 10 participants in Cohort 2, including PK modeling and simulation to further assess the RPV pediatric dose based on accumulating data, was discussed with and endorsed by the Independent Data Monitoring Committee (IDMC). At the time of Amendment 10, the following RPV dose recommendations applied to newly enrolled participants:

- RPV 25 mg PO QD for participants with a body weight of ≥25 kg
- RPV 15 mg PO QD for participants with a body weight of <25 kg

All ongoing participants in Cohort 2 (who were already in the post Week 48 treatment extension period at the time of Amendment 10) remained on the RPV 25 mg PO QD dose + two N(t)RTIs (investigator-selected), until roll-over to study IFD3004 was completed. All newly recruited participants started treatment with the weight-appropriate RPV dose stated above + two N(t)RTIs (investigator-selected), until they reached a total treatment duration of 48 weeks or discontinue earlier. To further evaluate and confirm the RPV dose for participants with lower body weights, newly enrolled participants with a body weight of <25 kg required intensive PK evaluation. Participants who experienced and were expected to continue experiencing clinical benefit from RPV and their background regimen comprising two investigator-selected N(t)RTIs at the end of the initial 48-week treatment period, could continue treatment (i.e., RPV + two N[t]RTIs) in the rollover study IFD3004.

Duration of Treatment

At least 48 weeks, or discontinued earlier.

Objectives (Cohort 2)

- To evaluate the steady-state PK (based on intensive PK analysis) of RPV 25 mg PO QD (participants with a body weight of ≥25 kg), 15 mg PO QD (participants with a body weight of <25 kg), or adjusted dose of RPV PO QD in participants aged ≥6 to <12 years.
- To evaluate short-term safety, tolerability and antiviral activity of RPV.
- To evaluate safety, tolerability and efficacy of RPV over a 48-week treatment period.
- To evaluate immunologic changes (as measured by $CD4^+$ cell parameters) over 48 weeks of treatment with RPV.
- To assess the evolution of viral genotype and phenotype over 48 weeks of treatment with RPV.
- To evaluate PK (by means of population PK) and PK-PD relationships for safety and efficacy of RPV.
- To evaluate treatment adherence as measured by the Study Adherence Questionnaire for Children and Teenagers.

Select Inclusion Criteria (Cohort 2)

1) Boy or girl, aged ≥6 to <12 years.
2) Participant weighing ≥17 kg.
3) Participant with documented HIV-1 infection.
4) Participant willing and able to give consent. In case the participant'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 participant will be informed about the trial and asked to give positive assent.
5) Participant can comply with the protocol requirements.
6) Participant had, 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 mother-to-child transmission (MTCT).
7) HIV-1 plasma RNA at screening ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL (assayed by RNA polymerase chain reaction standard specimen procedure).

8) In the judgment of the investigator, it is appropriate to initiate ART based on the participant'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) Participant 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 participants is determined to be <25 mg (only applicable for participants enrolled after it has been decided that a lower RPV dose is appropriate for participants up to a certain age or body weight).
11) The participant 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.

Exclusion Criteria

1) Any previous use of ARVs, with the exception of a single dose of NVP or up to 6 weeks of AZT use to prevent MTCT.
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 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) Participant 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 participants 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.
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) Participant 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
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
17) Any grade 3 or 4 laboratory toxicity according to the DAIDS grading table, 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 participants <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

Study Procedures

Two formulations of RPV were used in this study:

- The commercially available RPV was formulated as an oral film-coated tablet, containing 27.5 mg of RPV as the hydrochloric acid salt, equivalent to 25 mg of RPV as the free base.
- For adjusted weight-based dosing, RPV was formulated as a tablet containing 2.5 mg of RPV as the free base. The tablets must be dispersed prior to use.

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. RPV was initiated at baseline (Day 1). Thereafter, participants returned for visits at Week 1, Week 2, Week 4, then every 4 weeks until Week 16, every 8 weeks until Week 48.

Cohort 2: Children Aged ≥6 to <12 Years

For participants with a body weight of <25 kg, intensive pharmacokinetic sampling was performed during a 24-hour dosing interval at the Week 2 visit (between Day 14 to 18) and at the 2-weeks Post Switch visit, if applicable to evaluate the steady-state pharmacokinetic parameters of RPV. In all participants sparse pharmacokinetic sampling will be performed for population pharmacokinetic analysis.

Participants who experience and are expected to continue experiencing clinical benefit from RPV and their background regimen comprising two 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 rollover study IFD3004 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.

Statistical Analyses

The ITT population was defined as the set of all participants who have taken at least one dose of RPV, regardless of their compliance with the protocol and adherence to the dosing regimen.

Cohort 2: Children Aged ≥6 to <12 Years

An initial analysis was performed when the five Part 1 participants of the mini-cohort had been treated for at least 4 weeks (or discontinued earlier). This will be followed by an overall analysis when all Part 1 participants had been treated for at least 4 weeks (or discontinued earlier). The objective of these analyses was to determine whether it is appropriate to continue with the 25 mg PO QD dose for the treatment of children, based primarily on the PK of these participants and the antiviral activity and safety data. All available antiviral activity and safety data were included in these analyses, even if they have been obtained after the intensive PK sampling. The final analysis will was performed when all Cohort 2 participants 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.

Virologic Response

- Two consecutive measurements of <400 or <50 HIV-1 RNA copies/mL

Virologic Failure

- Lack of Response
  - Confirmed decrease in plasma VL of <1.0 $\log_{10}$ at Week 12 from the baseline VL
- Loss of Response:
  - Two consecutive measurements of ≥400 HIV-1 RNA copies/mL after having been confirmed virologic responder (defined as 2 consecutive measurements of <50 copies/mL)

Suspected Virologic Failure

- HIV-1 RNA ≥200 copies/mL after confirmed HIV-1 RNA of <50 copies/mL

13.2. Study TMC278HTX2002 (HTX2002)

Title

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

Study Design

This was a phase 2, open-label, single-arm, multicenter study performed to evaluate the PK, safety, tolerability, and efficacy (antiviral activity) of RPV in combination with other ARVs in HIV-1-infected, virologically suppressed (HIV-1 RNA <50 copies/mL) children aged ≥2 to <12 years with body weight ≥10 kg and without a history of virologic failure or documented resistance to RPV.

Intensive PK data were gathered in HIV-1-infected children with body weight of <25 kg (regardless of age) to further identify an RPV dose that provides exposures similar to those in adults. A commercially available oral RPV 25 mg tablet formulation and an investigational oral 2.5 mg tablet formulation was used in this study.

An HTX2002 substudy was performed to support the refinement of a population PK model across age groups (children, adolescents, and adults) combining data from studies in treatment-naïve (from StudyC213) and virologically-suppressed participants (from Study HTX2002). In the substudy, intensive PK data were collected from a subset of participants aged ≥6 years with body weight ≥25 kg. While all PK data from Study HTX2002 and Study C213 Cohort 2 were combined in a population PK model to accommodate regulatory requirements.

Duration of Treatment

At least 48 weeks, or discontinued earlier.

Objectives

Primary Objectives

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

Secondary Objectives

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

Select Inclusion Criteria

1. Aged ≥2 to <12 years at screening.
2. Criterion modified per Amendment 3

   2.1 Weighing at least 10 kg at screening.
3. Have documented chronic HIV-1 infection.
4. Criterion modified per Amendment 1 and Amendment 2
   4.1 On a stable ARV regimen for at least 6 months prior to screening and virologically suppressed with documented evidence of at least two plasma viral loads <50 HIV-1 RNA copies/mL: one within 2 to 12 months prior to screening and one at screening.
5. Parent(s) (preferably both if available or as per local requirements) (or the participant's legally acceptable representative[s]) must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is willing to allow the child to participate in the study. Assent is also required from participants capable of understanding the nature of the study (typically aged ≥7 years).
6. Can comply with the protocol requirements.
7. Can switch from any ARV class.
8. Never been treated with a therapeutic HIV vaccine.
9. Otherwise healthy and medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.
10. Otherwise healthy on the basis of clinical laboratory tests performed at screening. If the results of biochemistry, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and

reasonable for the study population. This determination must be recorded in the participant's source documents and initialed by the investigator.

11. Historical HIV-1 genotyping result at screening for children aged ≥2 to <6 years (and for children aged ≥6 to <12 years if a historical HIV-1 genotyping result is available at screening) must demonstrate sensitivity to RPV and to the selected background ARVs.
12. Girls are eligible to participate if they are not pregnant and not breastfeeding.
13. Girls of childbearing potential must have a negative highly sensitive serum β-human chorionic gonadotropin test at screening.
14. Heterosexually active girls of childbearing potential must practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method while receiving study treatment and for at least 30 days after last RPV intake.
15. Heterosexually active boys must practice a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method while receiving study treatment and for at least 30 days after last RPV intake. All HIV-1-infected boys are advised to use a condom to reduce the risk of transmitting HIV

Exclusion Criteria

1. Have previously documented HIV-2 infection.
2. Have known or suspected acute (primary) HIV-1 infection.
3. Taken any disallowed concomitant therapies within 4 weeks before the planned first dose of study intervention.
4. A positive HLA-B*5701 test at screening (when the investigator considers ABC in the background regimen). In case of a positive test, ABC cannot be administered, but instead, the investigator can select another ARV in the background regimen. HLA-B*5701 testing is not required for participants with prior documented negative results.
5. Any current or history of adrenal disorder.
6. Any active clinically significant diseases (e.g., pancreatitis, cardiac dysfunction, active and significant psychiatric disorders, clinical suspicion of adrenal insufficiency, and hepatic impairment) or findings at screening or medical history that, in the investigator's opinion, would compromise the outcome of the study.
7. A history of virologic failure to ARVs with or without availability of an HIV-1 genotype result at the time of failure.
8. Documented genotypic evidence of resistance to RPV or to the selected background ARVs from historical data available in the source documents (i.e., at least one NNRTI RAM from the following list compiled on the basis of the list of the International Antiviral Society United States of America [IAS-USA] NNRTI RAMs and other relevant publications).

A098G	V106M	Y181C	G190S
L100I	V108I	Y181I	G190T
K101E	E138A	Y181V	P225H
K101P	E138G	Y188C	F227C
K101Q	E138K	Y188H	M230I

K103H	E138Q	Y188L	M230L
K103N	E138R	G190A	P236L
K103S	V179E	G190C	K238N
K103T	V179D	G190E	K238T
V106A	V179T	G190Q	Y318F

9. A known clinically significant allergy, hypersensitivity, or intolerance to RPV or its excipients or to the selected background ARVs.
10. Criterion modified per Amendment 1:
    10.1 Received an investigational intervention (including investigational vaccines) containing an active substance or used an invasive investigational medical device within 90 days before the planned first dose of study intervention.
11. Enrolled in clinical studies that include any blood sampling with a volume >50 mL taken within 6 months before the planned first administration of RPV, specimen collection, or other interventional procedure. Concurrent participation in non-interventional observational studies is allowed as long as there is no impact on the objectives of this study. Data collected in this study can be reported in the observational study.
12. Any condition (including but not limited to the abuse of alcohol or drugs [e.g., barbiturates, opiates, cocaine, cannabinoids, amphetamines, and benzodiazepines]) for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
13. A life expectancy of less than 6 months.
14. Any currently active AIDS-defining illness or Stage-3-defining Opportunistic Illnesses in HIV Infection (cut-off for Stage-3 illnesses is 6 years of age per criteria from 2014).
15. Any grade 3/4 laboratory abnormality at screening according to the Division of AIDS (DAIDS) grading table, except for a selection of abnormalities:

    a) Grade 3 absolute neutrophil count

    b) Grade 3 platelets

    c) Grade 3 glucose elevation in diabetics

    d) asymptomatic Grade 3 pancreatic amylase elevation

    e) asymptomatic Grade 3 triglyceride / cholesterol / glucose elevation

    f) asymptomatic Grade 4 triglyceride elevation

16. Active tuberculosis or being treated for tuberculosis with rifamycins at screening.
17. The following ECG findings at screening, if judged clinically significant by the investigator: abnormal pulse rate and QRS intervals; rhythm abnormalities; evidence of acute ischemic changes.
18. Criterion modified per Amendment 3

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

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

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

c) evidence of ventricular pre-excitation.

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

e) evidence of second or third degree heart block.

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

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

h) personal or family history of long QT syndrome.

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

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

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

19. Acute clinical hepatitis at screening.

Study Procedures

Two formulations of RPV were used in this study:

- The commercially available RPV was formulated as an oral film-coated tablet, containing 27.5 mg of RPV as the hydrochloric acid salt, equivalent to 25 mg of RPV as the free base.
- For 15 mg, 12.5 mg, or another adjusted weight-based dosing, RPV was formulated as a tablet containing 2.75 mg of RPV as the hydrochloric acid salt, equivalent to 2.5 mg of RPV as the free base. The tablets must be dispersed prior to use.

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

Statistical Analyses

All statistical analysis will be performed on the intent-to-treat population, defined as all participants who receive at least one dose of RPV. The primary analysis (with formal database lock) will be done when all participants have reached Week 24 (or discontinued earlier). The final analysis (with formal database lock) will be done when all participants have reached Week 48 (or discontinued earlier).

Suspected Virologic Failure

- HIV-1 RNA ≥200 copies/mL

Virologic Failure

- Loss of Response
- Two consecutive measurements of ≥200 HIV-1 RNA copies/mL at least 2 weeks apart after having been confirmed virologic responder (defined as 2 consecutive measurements of <50 copies/mL)

14. Efficacy: Additional Information and Assessment

Table 24. Virologic Outcomes for Week 48 (Snapshot Analysis) Full Analysis Set, by Dose-Weight Group, Study C213 Cohort 2

	rilpivirine					
	12.5 mg qd, <20kg	15 mg qd, 20-<25kg	25 mg qd, <25kg	25 mg qd, >=25kg	All RPV Recommended Dose	All Participants
Analysis set: Full Analysis Set	2	2	5	9	13	18
Snapshot Outcome (<50 copies/ml) 48-week initial treatment period, n(%) (95% CI)						
N	2	2	5	9	13	18
Virologic Response (< 50 copies/mL)	1 (50.0%) (1.26;98.74)	0	4 (80.0%) (28.36;99.49)	8 (88.9%) (51.75;99.72)	9 (69.2%) (38.57;90.91)	13 (72.2%) (46.52;90.31)
Virologic Failure	1 (50.0%) (1.26;98.74)	0	1 (20.0%) (0.51;71.64)	1 (11.1%) (0.28;48.25)	2 (15.4%) (1.92;45.45)	3 (16.7%) (3.58;41.42)
HIV RNA ≥ 50 copies/mL	1 (50.0%) (1.26;98.74)	0	1 (20.0%) (0.51;71.64)	0	1 (7.7%) (0.19;36.03)	2 (11.1%) (1.38;34.71)
Virologic failure - leading to discontinuation	0	0	0	0	0	0
Virologic failure – discontinued due to other reason[a] and last available HIV RNA ≥ 50 copies/mL	0	0	0	1 (11.1%) (0.28;48.25)	1 (7.7%) (0.19;36.03)	1 (5.6%) (0.14;27.29)
Virologic failure - switch in background regimen not permitted by the protocol	0	0	0	0	0	0
No viral load data in time window	0	2 (100.0%) (15.81;100)	0	0	2 (15.4%) (1.92;45.45)	2 (11.1%) (1.38;34.71)
Missing data during window but on study	0	2 (100.0%) (15.81;100)	0	0	2 (15.4%) (1.92;45.45)	2 (11.1%) (1.38;34.71)
Discontinued due to other reason and last available HIV RNA < 50 copies/mL	0	0	0	0	0	0
Discontinued due to AE/death	0	0	0	0	0	0

Note: N = number of participants with data, n = number of participants with that observation.
Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
RPV Recommended dose: 12.5 mg for <20 kg, 15 mg QD for 20 to <25 kg, 25 mg QD for ≥25 kg.
[a] Other reason specified as reaching a virologic endpoint.
Abbreviations: CI, Clopper-Pearson confidence interval; RPV, rilpivirine; qd, once daily. Source: Applicant's Summary of Clinical Study Final Report (Table 10, p. 53).

15. Clinical Safety: Additional Information and Assessment

Table 25. All Treatment Emergent Adverse Events by System Organ Class; Full Analysis Set, *Through Week 48*, Study C213 Cohort 2

System Organ Class Preferred Term	12.5 mg QD, <20 kg N = 2 n (%)	15 mg QD, 20 - <25 kg N = 2 n (%)	25 mg QD, <25 kg N = 5 n (%)	25 mg QD, >= 25 kg N = 9 n (%)	All RPV Recommended Dose N = 13 n (%)	All Participants N = 18 n (%)
Any Adverse Event	2 (100.0)	2 (100.0)	5 (100.0)	8 (88.9)	12 (92.3)	17 (94.4)
Infections and infestations	**2 (100.0)**	**2 (100.0)**	**5 (100.0)**	**7 (77.8)**	**11 (84.6)**	**16 (88.9)**
Upper respiratory tract infection	2 (100.0)	2 (100.0)	3 (60.0)	5 (55.6)	9 (69.2)	12 (66.7)
Otitis media	1 (50.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (7.7)	2 (11.1)
Conjunctivitis	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Folliculitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Fungal infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Herpes simplex	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Impetigo	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Lower respiratory tract infection	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (5.6)
Malaria	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (5.6)
Oral herpes	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Pharyngitis	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Pneumonia	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Tonsillitis	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**2 (40.0)**	**2 (22.2)**	**2 (15.4)**	**4 (22.2)**
Decreased appetite	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (7.7)	2 (11.1)
Hyperkaliemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Hypokalemia	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Blood and lymphatic system disorders	**0 (0.0)**	**1 (50.0)**	**1 (20.0)**	**1 (11.1)**	**2 (15.4)**	**3 (16.7)**
Anemia	0 (0.0)	1 (50.0)	1 (20.0)	0 (0.0)	1 (7.7)	2 (11.1)
Iron deficiency anemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**2 (22.2)**	**2 (15.4)**	**3 (16.7)**
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (15.4)	2 (11.1)

System Organ Class Preferred Term	12.5 mg QD, <20 kg N = 2 n (%)	15 mg QD, 20 - <25 kg N = 2 n (%)	25 mg QD, <25 kg N = 5 n (%)	25 mg QD, >= 25 kg N = 9 n (%)	All RPV Recommended Dose N = 13 n (%)	All Participants N = 18 n (%)
Any Adverse Event	2 (100.0)	2 (100.0)	5 (100.0)	8 (88.9)	12 (92.3)	17 (94.4)
Vomiting	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (7.7)	2 (11.1)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Constipation	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Nausea	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Toothache	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Investigations	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**2 (22.2)**	**2 (15.4)**	**3 (16.7)**
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (7.7)	2 (11.1)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	1 (20.0)	1 (11.1)	1 (7.7)	2 (11.1)
ACTH stimulation test abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Electrocardiogram qt prolonged	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	**1 (50.0)**	**0 (0.0)**	**0 (0.0)**	**2 (22.2)**	**3 (23.1)**	**3 (16.7)**
Cough	1 (50.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (15.4)	2 (11.1)
Rhinitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Skin and subcutaneous tissue disorders	**1 (50.0)**	**1 (50.0)**	**0 (0.0)**	**1 (11.1)**	**3 (23.1)**	**3 (16.7)**
Rash	1 (50.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (15.4)	2 (11.1)
Dermatitis atopic	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (5.6)
Cardiac disorders	**0 (0.0)**	**1 (50.0)**	**0 (0.0)**	**1 (11.1)**	**2 (15.4)**	**2 (11.1)**
Rheumatic heart disease	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (7.7)	1 (5.6)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Nervous system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (11.1)**	**1 (7.7)**	**1 (5.6)**
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)

Source: Clinical Reviewer; OCS Analysis Studio, Safety Explorer.
Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 25.0.
n = number of participants with that particular AE; % = percentage of participants with that particular AE against the total number of participants.
Denominator for post Week 48 treatment extension period is the number of participants who enrolled in this treatment period.
Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
RPV Recommended dose: 12.5 mg QD for <20kg, 15 mg QD for 20 - <25kg, 25 mg QD for >=25 kg.
Abbreviations: QD, once daily; RPV, rilpivirine

Table 26. All Treatment Emergent Adverse Events by System Organ Class; Full Analysis Set, *Post-Week 48*, Study C213 Cohort 2

System Organ Class Preferred Term	12.5 mg QD, <20 kg N = 2 n (%)	15 mg QD, 20 - <25 kg N = 2 n (%)	25 mg QD, <25 kg N = 5 n (%)	25 mg QD, >= 25 kg N = 9 n (%)	All RPV Recommended Dose N = 13 n (%)	All Participants N = 18 n (%)
Any Adverse Event	0 (0.0)	1 (50.0)	2 (40.0)	4 (44.4)	5 (38.5)	7 (38.9)
Infections and infestations	**0 (0.0)**	**1 (50.0)**	**2 (40.0)**	**3 (33.3)**	**4 (30.8)**	**6 (33.3)**
Upper respiratory tract infection	0 (0.0)	1 (50.0)	1 (20.0)	3 (33.3)	4 (30.8)	5 (27.8)
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Oral herpes	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Respiratory tract infection	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**0 (0.0)**	**0 (0.0)**	**1 (5.6)**
Iron deficiency anemia	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**0 (0.0)**	**0 (0.0)**	**1 (5.6)**
Diarrhoea	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Hemorrhoids	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Toothache	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (11.1)**	**1 (7.7)**	**1 (5.6)**
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Psychiatric disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (11.1)**	**1 (7.7)**	**1 (5.6)**
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Renal and urinary disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (11.1)**	**1 (7.7)**	**1 (5.6)**
Proteinuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (7.7)	1 (5.6)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**0 (0.0)**	**0 (0.0)**	**1 (5.6)**
Dermatitis	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.6)

Source: Clinical Reviewer; OCS Analysis Studio, Safety Explorer.
Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 25.0.
n = number of participants with that particular AE; % = percentage of participants with that particular AE against the total number of participants.
Denominator for post Week 48 treatment extension period is the number of participants who enrolled in this treatment period.
Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
RPV Recommended dose: 12.5 mg QD for <20kg, 15 mg QD for 20 - <25kg, 25 mg QD for >=25 kg.
Abbreviations: QD, once daily; RPV, rilpivirine.

Table 27. All Treatment Emergent Adverse Events by System Organ Class; Full Analysis Set, *Through Week 48*, Study HTX2002

System Organ Class Preferred Term	12.5 mg QD, <20 kg N = 1 n (%)	15 mg QD, <20 kg N = 2 n (%)	15 mg QD, 20 - <25 kg N = 5 n (%)	25 mg QD, >=25 kg N = 18 n (%)	All RPV Recommended Dose N = 24 n (%)	All Participants N = 26 n (%)
Any Adverse Event	1 (100.0)	0 (0.0)	5 (100.0)	12 (66.7)	18 (75.0)	18 (69.2)
Gastrointestinal disorders	**1 (100.0)**	**0 (0.0)**	**2 (40.0)**	**5 (27.8)**	**8 (33.3)**	**8 (30.8)**
Vomiting	1 (100.0)	0 (0.0)	1 (20.0)	2 (11.1)	4 (16.7)	4 (15.4)
Abdominal pain	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)	2 (8.3)	2 (7.7)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	2 (8.3)	2 (7.7)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Aphthous ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Dental caries	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (4.2)	1 (3.8)
Frequent bowel movements	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Odynophagia	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Infections and infestations	**1 (100.0)**	**0 (0.0)**	**2 (40.0)**	**4 (22.2)**	**7 (29.2)**	**7 (26.9)**
Rhinitis	1 (100.0)	0 (0.0)	0 (0.0)	1 (5.6)	2 (8.3)	2 (7.7)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)	2 (8.3)	2 (7.7)
Asymptomatic covid-19	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Ear infection	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	1 (3.8)
Fungal skin infection	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (4.2)	1 (3.8)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Malaria	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (4.2)	1 (3.8)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Otitis media	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Investigations	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**5 (27.8)**	**6 (25.0)**	**6 (23.1)**
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (16.7)	3 (12.5)	3 (11.5)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	2 (8.3)	2 (7.7)
Blood insulin increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Cortisol decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Electrocardiogram qt prolonged	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	1 (3.8)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Nervous system disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**4 (22.2)**	**5 (20.8)**	**5 (19.2)**

System Organ Class Preferred Term	12.5 mg QD, <20 kg N = 1 n (%)	15 mg QD, <20 kg N = 2 n (%)	15 mg QD, 20 - <25 kg N = 5 n (%)	25 mg QD, >=25 kg N = 18 n (%)	All RPV Recommended Dose N = 24 n (%)	All Participants N = 26 n (%)
Any Adverse Event	1 (100.0)	0 (0.0)	5 (100.0)	12 (66.7)	18 (75.0)	18 (69.2)
Headache	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)	2 (8.3)	2 (7.7)
Amnesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**3 (16.7)**	**4 (16.7)**	**4 (15.4)**
Nasal congestion	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)	2 (8.3)	2 (7.7)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
General disorders and administration site conditions	**1 (100.0)**	**0 (0.0)**	**0 (0.0)**	**2 (11.1)**	**3 (12.5)**	**3 (11.5)**
Pyrexia	1 (100.0)	0 (0.0)	0 (0.0)	1 (5.6)	2 (8.3)	2 (7.7)
Injection site pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**2 (11.1)**	**3 (12.5)**	**3 (11.5)**
Decreased appetite	0 (0.0)	0 (0.0)	1 (20.0)	1 (5.6)	2 (8.3)	2 (7.7)
Folate deficiency	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Hyperglycemia	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (4.2)	1 (3.8)
Blood and lymphatic system disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**1 (5.6)**	**2 (8.3)**	**2 (7.7)**
Lymphadenopathy	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (4.2)	1 (3.8)
Macrocytosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Injury, poisoning and procedural complications	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**1 (5.6)**	**2 (8.3)**	**2 (7.7)**
Arthropod bite	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (4.2)	1 (3.8)
Contusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (11.1)**	**2 (8.3)**	**2 (7.7)**
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Joint swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Muscle contracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Osteochondrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**2 (11.1)**	**2 (8.3)**	**2 (7.7)**
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Nail pigmentation	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)

System Organ Class Preferred Term	12.5 mg QD, <20 kg N = 1 n (%)	15 mg QD, <20 kg N = 2 n (%)	15 mg QD, 20 - <25 kg N = 5 n (%)	25 mg QD, >=25 kg N = 18 n (%)	All RPV Recommended Dose N = 24 n (%)	All Participants N = 26 n (%)
Any Adverse Event	1 (100.0)	0 (0.0)	5 (100.0)	12 (66.7)	18 (75.0)	18 (69.2)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Ear and labyrinth disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (5.6)**	**1 (4.2)**	**1 (3.8)**
Ear pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Eye disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (5.6)**	**1 (4.2)**	**1 (3.8)**
Conjunctivitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)
Immune system disorders	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**0 (0.0)**	**1 (4.2)**	**1 (3.8)**
Food allergy	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (4.2)	1 (3.8)
Psychiatric disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (5.6)**	**1 (4.2)**	**1 (3.8)**
Attention deficit hyperactivity disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	1 (4.2)	1 (3.8)

Source: Clinical Reviewer; OCS Analysis Studio, Safety Explorer.
Participants are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 25.1.
n = number of participants with that particular AE; % = percentage of participants with that particular AE against the total number of participants.
RPV dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
RPV Recommended dose: 12.5 mg QD for <20kg, 15 mg QD for 20 - <25 kg, 25 mg QD for >=25 kg.
Abbreviations: QD, once daily; RPV, rilpivirine.

16. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Bioanalytical site inspection has been requested for a phase 1 Study TMC278IFD1008, which assessed the relative bioavailability of new pediatric formulation, 2.5 mg RPV tablet for oral suspension, compared to the currently approved 25 mg tablet formulation. Bio-analytical site inspection was also requested for Study C213 Cohort 2 and HTX2002, which are pivotal phase 2 efficacy and safety studies in pediatrics. PK data from these studies are pivotal to bridge the efficacy between pediatrics and adults. The bioanalytical site is same as the site for TMC278IFD1008. The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed because a Remote Regulatory Assessment (RRA) for the site was conducted in February 2023 with no major concerns.

17. Labeling Summary of Considerations and Key Additional Information

The USPI and PPI (Patient Package Insert) have been agreed to and the main changes are summarized below.

The labeling has been updated to reflect changes in the indication:

- Extending the population to treatment-naïve pediatric patients weighing at least 25 kg, and with HIV RNA ≤100,000 at start of therapy for Edurant 25 mg tablets.
- Extending the population to treatment-naïve pediatric patients at least 2 years of age, weighing at least 14 kg, and with HIV RNA ≤100,000 at start of therapy for Edurant PED 2.5 mg tablets for oral suspension.

Overall Major Changes

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 5347394

(b) (4)

18. Postmarketing Requirements and Commitments

The current submission fulfills the Pediatric Written Request and no additional pediatric postmarketing study requirements or postmarketing commitments will be sought. The current submission also fulfills the following Post Marketing Requirement under Pediatric Research Equity Act (PREA):

1982-3 Conduct a study in HIV-1 infected patients 2 years to <12 years old who are either treatment-naïve or virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of rilpivirine. Study participants must be monitored for a minimum of 24 weeks to assess durability of antiviral response.

19. Financial Disclosure

The Applicant has submitted Form FDA 3454, which certifies that they (Applicant) did not enter into any financial relationships with principle or sub-investigators. The form included an attachment containing the names of principal investigators and sub-investigators for Study 2C13 and Study HTX2002 who have attested to the absence of financial interests or arrangements described in 21 CFR Part 54.4(a)(3).

Table 28. Covered Clinical Studies: C213 and HTX2002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 20 (Study C213) and 52 (Study HTX2002)		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		

20. References

1. World Health Organization (WHO). HIV Data and Statistics. Available at: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics. Accessed February 27, 2024.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed February 27, 2024.
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5. IMPAACT 2036. Study of Oral and Long-Acting Injectable Cabotegravir and Rilpivirine in Virologically Suppressed Children Living With HIV-1, Two to Less Than 12 Years of Age. NCT05660980; Available at https://clinicaltrials.gov/study/NCT05660980 and https://www.impaactnetwork.org/studies/impaact2036. Accessed February 27, 2024.

21. Review Team

Table 29. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	London Harrison, MBEE
Nonclinical Reviewer	Ilona Bebenek, PhD
Nonclinical Team Leader	Laine Peyton Myers, PhD
Office of Clinical Pharmacology Reviewers	Huimin Zheng, PhD.; Elyes Dahmane, PhD
Office of Clinical Pharmacology Team Leader(s)	Su-Young Choi PharmD., PhD; Justin C. Earp, PhD.
Clinical Reviewer	Timothy Jancel, PharmD, MHS, BCPS, BCIDP
Clinical Team Leader	Benjamin Lorenz, MD
Clinical Virology Reviewer	Lisa Naeger, PhD
Clinical Virology Team Leader	Jules O'Rear, PhD
Associate Director for Labeling	Stacey Min, PharmD
Cross-Disciplinary Team Leader	Benjamin Lorenz, MD
Associate Director for Therapeutic Review	Yodit Belew, MD

Table 30. Additional Reviewers of Application

Office or Discipline	Name(s)
CMC ATL	Molly Lee
Drug Product	Akshata Nevrekar (TL: David Claffey)
Drug Substance	Daniel Chan (TL: Katherine Windsor)
Biopharmaceutics	Hardikkumar Patel (Elsbeth Chikhale)
Process/Facility	Naveen Kanthamneni (Hang Guo)
RBPM	Omolara Oyinlola-Adeyemi
OPDP	Jessica Chung (TL: Brantley Dorch)
PLT	Wendy Lubarsky
OSE/DMEPA	Amy Bao (TL: Yevgeniya (Jen) Kogan)
OSE/DMEPA	Melina Fanari (TL: Madhuri Patel)

Abbreviations: ATL, Application Technical Lead; CMC, chemistry, manufacturing, and controls; DMEPA, Division of Medication Error Prevention and Analysis; NDA, new drug application; OPDP, Office of Prescription Drug Promotion; OSE, Office of Surveillance and Epidemiology; RBPM, Regulatory Business Project Manager; TL, Team Lead.

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/s/

TIMOTHY J JANCEL
03/15/2024 04:19:01 PM

HUIMIN ZHENG
03/15/2024 04:39:48 PM

ELYES DAHMANE
03/15/2024 04:41:34 PM

SU-YOUNG CHOI
03/15/2024 04:43:40 PM
Dr. Justin Earp (pharmacometrics TL) reviewed the document and concurred.

BENJAMIN D LORENZ
03/15/2024 04:46:52 PM