Pharmacokinetics, Safety, Tolerability and Antiviral Activity of Switching to Oral Rilpivirine in Combination With Other Antiretroviral Therapy in Virologically Suppressed Children Living With HIV-1 Infection

Forty-eight-week Results From the Phase 2, Open-label, Single-arm, PICTURE Study

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Background: PICTURE (NCT04012931) was a phase 2, open-label, single-arm, multicenter study evaluating pharmacokinetics (PK), safety, tolerability and antiviral activity of oral rilpivirine in combination with other antiretroviral therapy (ART) in children living with HIV-1 with virologic suppression.

Methods: Children (≥2 to <12 years, ≥10 kg) living with HIV-1, virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ART were enrolled. Weight-based rilpivirine [25 mg once-daily (qd) for ≥25 kg, 15 mg (6 × 2.5 mg) qd for 20 kg to <25 kg and 12.5 mg (5 × 2.5 mg) qd for 10 to <20 kg in film-coated or investigational dispersible tablet formulations] was administered orally in combination with background ART for 48 weeks. The primary objectives were evaluation of rilpivirine steady-state PK, determination of an appropriate weight-based dose, and safety and tolerability when combined with other ARTs. Results of the primary (week 24) and final (week 48) analyses are presented.

Results: Of 40 participants screened, 26 (65%) were enrolled and treated with rilpivirine. All participants completed the week 48 visit and were included in the final analysis. PK parameters were observed to be in the target range for all rilpivirine weight-based doses. Through week 48, 19/26 (73.1%) participants had ≥1 adverse event; all grade 1–2 and none were treatment related. All 26 participants (100%) receiving rilpivirine in combination with ART remained virologically suppressed at both weeks 24 and 48. Adherence to treatment was 98.99%.

Conclusion: Rilpivirine in combination with background ART was well-tolerated and maintained virologic suppression from baseline through week 48 in the studied population of children living with HIV-1. Rilpivirine exposure was within the target range for all doses.

Key Words: antiretroviral therapy, children, HIV-1, pharmacokinetics, rilpivirine, safety

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INTRODUCTION

Children living with HIV-1 (CLHIV) face significant risks of mortality and morbidity, aggravated by limited access to treatment.[1] According to the Joint United Nations Program on HIV/AIDS (UNAIDS) Global AIDS Update-2022, only 57% of children ages 0–14 years get access to lifesaving treatment compared to 77% of adults receiving antiretroviral therapy (ART).[2] In response to the urgent challenges posed by the HIV epidemic, a global alliance comprised of UNAIDS, the United Nations International Children's Emergency Fund, the World Health Organization (WHO) and partnering organizations has undertaken an initiative to ensure that all CLHIV receive treatment by the end of the decade.[2]

Pediatric HIV treatment guidelines are often based on experience in adult patients or expert opinions with relatively scarce data from trials in children.[3] According to the WHO, CLHIV continue to have lower rates of viral suppression than adults.[4] Furthermore, child-friendly formulations of the newest and most effective antiretrovirals available for adults are lacking.[5,6]

In 2015, the WHO recommended initiating ART for all children and adolescents living with HIV, regardless of clinical stage

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The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. Requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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or CD4+ T-lymphocyte (CD4) count, resulting in increased ART coverage and reduced HIV-related morbidity and mortality.[7] Based on the UNAIDS estimate for 2023, efforts to reach the 1.4 million CLHIV aged <14 years are falling well short of the 95-95-95 testing and treatment targets, with only 66% (47%–87%) of CLHIV having their HIV infection diagnosed, 86% (62% to >98%) of those diagnosed receiving ART, and 84% (60% to >98%) of those on ART achieving viral suppression.[2]

Available ART regimens include 2 or more drugs from different classes, such as HIV protease inhibitors (PIs), nonnucleoside and nucleoside reverse transcriptase inhibitors (NNRTIs and NRTIs), and integrase strand transfer inhibitors (INSTIs) to effectively inhibit HIV replication and slow disease progression.[8] Current guidelines include INSTI-based treatment regimens as preferred first-line ART.[9] Nevertheless, NNRTI-based treatment regimens have shown potent and long-lasting antiviral activity.[10–12] Rilpivirine (RPV), a second-generation NNRTI, proved to be noninferior to efavirenz in 2 double-blind phase 3 studies (ECHO and THRIVE) that compared RPV with 2 NRTIs versus efavirenz with 2 NRTIs in treatment-naïve adults.[13] Despite the relatively high viral loads measured in newly diagnosed infants and the use of nevirapine in infants born to women with HIV infection to prevent mother-to-child-transmission, second-generation NNRTIs, such as RPV, could offer alternative treatment options for both treatment-naïve and antiretroviral-experienced pediatric patients.[6,14]

The use of RPV in combination with other antiretroviral drugs (ARVs) in adolescents (ages ≥12 to <18 years) with baseline plasma HIV-1 RNA ≤100,000 copies/mL was supported by the 48-week analysis of Cohort 1 in the phase 2 PAINT study.[15] The 25-mg oral tablet formulation of RPV, in combination with other ARVs, has been approved since 2015 for use in ARV treatment-naïve patients aged ≥12 years with plasma HIV-1 RNA ≤100,000 copies/mL in the United States (US), the European Union and many other countries.[16,17] Recently, based on the results of the analyses of the data of Cohort 2 in the phase 2 PAINT study and the data of the PICTURE study (NCT04012931)[18] a weight-based dosing of RPV was approved in the US and EU for use in children (treatment-naïve-only in the US) ages ≥2 years, with plasma HIV-1 RNA ≤100,000 copies/mL and weighing ≥14 kg.[16,17]

Here, we report the primary (week 24) and final (week 48) results from the phase 2, noncomparative PICTURE study which evaluated the pharmacokinetics (PK), safety, tolerability, and antiviral activity of RPV in combination with other ARVs in virologically suppressed (plasma HIV-1 RNA <50 copies/mL) children ages ≥2 to <12 years living with HIV-1.

METHODS

This phase 2, multicenter, open-label, single-arm, interventional, PICTURE study was conducted from July 23, 2019 (date first participant was screened) to February 17, 2023 (last participant's last visit) across 10 centers in Italy (3 sites), South Africa (1 site), Spain (1 site), Thailand (3 sites), Portugal (1 site) and Uganda (1 site). The study was approved by the institutional review board/institutional ethics committee at each study center (Table, Supplemental Digital Content 1, https://links.lww.com/INF/G330). All participants or their legally authorized representative provided written informed consent in accordance with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice.

Study Participants

Children with chronic HIV-1 infection, ages ≥2 to <12 years, weighing ≥10 kg, virologically suppressed (plasma HIV-1 RNA <50 copies/mL) on a stable ART regimen for at least 6 months, and having no history of virologic failure to ARVs were included in the study. Participants with a history of HIV-2 infection, known or suspected primary acute HIV-1 infection, positive HLA-B*5701 test (when the investigator considers abacavir in the background regimen [abacavir could be replaced with another antiretroviral drug]), active AIDS-defining illness or stage-3-defining opportunistic illnesses, or one or more risk factors for QTc prolongation were excluded. Additionally, participants with a history of virologic failure to ARVs (with/without the availability of an HIV-1 genotype result at the time of failure), and genotypic evidence of resistance to RPV or to the selected background ARVs were excluded.

Study Design and Treatment

All participants underwent a screening phase for a minimum of 6 weeks. RPV, at an adjusted weight-based dose, was administered orally once daily (qd) in combination with an investigator-selected background regimen (NRTIs or integrase inhibitors). Two formulations of RPV were used. A commercially available RPV 25-mg tablet (Edurant®) was used for the administration of the 25-mg dose, while an investigational RPV 2.5-mg dispersible tablet was used for the lower doses. All RPV doses were administered with a meal. On intensive PK days, RPV was administered within 40 minutes following the start of a standard breakfast. Based on all available RPV PK data, and upon the recommendation of the Independent Data Monitoring Committee (IDMC), RPV doses evolved during the PICTURE study to weight-based, once-daily dosing (25 mg for ≥25 kg, 15 mg for ≥20 to <25 kg and 12.5 mg for <20 kg). All participants received the study intervention until they reached a total treatment duration of 48 weeks (or discontinued earlier). Upon study completion, participants who continued to experience clinical benefits from treatment were offered enrollment in an open-label pediatric rollover study (NCT02494986).

Primary Objectives

RPV PK at steady-state derived from intensive PK assessments (Methods, Supplemental Digital Content 2, https://links.lww.com/INF/G330), determination of the appropriate weight-based dose of RPV, and the safety and tolerability in combination with other ARTs over a 24-week treatment period were primary objectives. Safety assessments included the incidence of grade 3 and 4 adverse events (AEs), serious AEs, HIV-related AEs and AEs leading to discontinuation of study intervention through week 24. AEs of interest were also recorded and included the following events of interest: endocrine, potential QTc interval prolongation, hepatic, neuropsychiatric and skin. Medical Dictionary for Regulatory Activities version 25.1 was used for coding of AEs. The Division of AIDS severity grading list (version 2.1) was used to grade AEs and laboratory abnormalities.

Secondary and Exploratory Objectives

Key secondary objectives were safety and tolerability over 48 weeks and antiviral activity (over 24 and 48 weeks), as evaluated by the proportion of participants with plasma HIV-1 RNA <50 and ≥50 copies/mL and <400 and ≥400 copies/mL, and absolute and relative change in CD4 count. Other secondary endpoints included population PK (popPK) based on intensive and sparse PK assessments (Methods, Supplemental Digital Content 2, https://links.lww.com/INF/G330), PK/pharmacodynamics relationship for safety and antiviral activity, resistance in the event of virologic failure (defined as 2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL), and treatment adherence (over 24 and 48 weeks).

Exploratory objectives included the assessment of palatability and swallowability of the 2.5- and 25-mg RPV tablets,

respectively (evaluated at week 2), and assessment of archived viral resistance. Antiretroviral resistance was assessed by peripheral blood mononuclear cell-based archived viral testing (GenoSure Archive assay). Other secondary assessments and patient-reported outcome measures are detailed in the Methods, Supplemental Digital Content 2, https://links.lww.com/INF/G330.

Dose Modification

The study was designed to adapt RPV doses based on the intensive PK data and changes in participants' body weight. To guide pediatric dosing, a minimum popPK-estimated geometric mean area under the concentration-time curve from 0 to 24 h (AUC_{24h}) of 1666 ng h/mL was targeted for pediatric patients, corresponding to 80% of the popPK-derived adult geometric mean AUC_{24h}. Dose adjustments were made when the participant's body weight changed from one weight band to another for which a different RPV dose was recommended (Methods, Supplemental Digital Content 2, https://links.lww.com/INF/G330). The decision to modify the RPV dose for a specific group of participants was made by the sponsor based upon the IDMC recommendation.

Antiviral Activity

The antiviral activity analyses were based on plasma HIV-1 RNA levels and CD4 counts. The proportions of participants with plasma HIV-1 RNA <50 and <400 copies/mL were analyzed using the FDA Snapshot algorithm at 24 and 48 weeks.[16] The absolute and relative change in CD4 counts were based on observed and imputed values.

Treatment Adherence

Treatment adherence was measured by drug accountability (pill count). Additionally, study-specific Adherence Questionnaires for Children and Caregivers (on file) were completed, adapted from the Pediatric European Network for the Treatment of AIDS.

Statistical Analysis

No formal sample size calculation was performed. The Full Analysis Set comprising participants who received at least one dose of RPV was used for all endpoint analyses in the final analysis at week 48. For intensive PK data, descriptive statistics were calculated for the plasma concentrations of RPV at each timepoint and for the derived PK parameters. Findings from clinical laboratory tests, physical examinations, vital signs and electrocardiogram were reported using descriptive statistics to summarize values and changes from baseline at each scheduled time point. Antiviral activity analyses were expressed as percentages with Clopper Pearson 95% CI at each time point. Participants who prematurely discontinued the study had their CD4 count imputed with the baseline value (resulting in a change of 0) and had last-observation-carried-forward imputation for intermediate missing values. Data on treatment adherence were summarized descriptively by dose-weight group and overall.

RESULTS

Study Population

Of the 40 participants screened, 26 (65%) were enrolled and all received at least one dose of RPV and were included in the Full Analysis Set. The most common reason for screening failure was ineligibility to fulfill inclusion [9/40 (22.5%)] and exclusion criteria [5/40 (12.5%)] (Table, Supplemental Digital Content 3, https://links.lww.com/INF/G330). At the final analysis, all enrolled participants had completed the study (week 48). Two (7.7%) participants had major protocol deviations (Results, Supplemental Digital Content 4, https://links.lww.com/INF/G330).

Most participants were male [16/26 (61.5%)], Black or African American [13/26 (50.0%)], with a median age of 9.9 years. Further details on participant demographics and baseline characteristics are presented in Table 1. One participant in the ≥2 to <6-year age group was previously receiving darunavir/ritonavir, raltegravir and lamivudine. In the ≥6 to <12-year age group, 11 participants previously received an NNRTI-based regimen (efavirenz, 9; nevirapine, 2), 7 received boosted PIs (lopinavir/ritonavir, 6; darunavir/ritonavir, 1) and 1 received a dolutegravir-based regimen. The most common NRTI background regimen during the study was lamivudine in combination with abacavir [20/26 (76.9%)] (Table, Supplemental Digital Content 5, https://links.lww.com/INF/G330).

Dose Modification

Based on interim PK, and safety and antiviral activity data at week 4 and week 12, and upon IDMC recommendation, the agreed dosing scheme was 12.5 mg qd (given as 5 × 2.5-mg tablets) for children with body weight <20 kg, 15 mg qd (given as 6 × 2.5-mg tablets) for children ≥20 to <25 kg, and 25 mg qd (given as 1 × 25-mg tablet) for those ≥25 kg. During the study, 3 participants received dose adjustments due to weight changes, 2 participants increased from 15 mg to 25 mg, and one participant increased from 12.5 to 15 mg.

Pharmacokinetics

Intensive PK data were available for 10 participants who received RPV treatment for 4 weeks: 12.5 mg qd (<20 kg, n = 2), 15 mg qd (<20 kg, n = 1; ≥20–<25 kg, n = 5) and 25 mg qd (≥25 kg, n = 2). The mean maximum plasma concentrations (C_{max}) were reached around 4–6 hours postdose (Fig. 1). Maximum plasma concentration (C_{max}) and AUC_{24h} at steady-state were similar at a recommended dose of 12.5 mg qd (<20 kg), and 15 mg qd (≥20–<25 kg), and at a higher dose of 15 mg qd (<20 kg), while they were like slightly higher at a recommended dose of 25 mg qd (≥25 kg) (Table 2). A popPK model, combining PK data from the current PICTURE study with PK data from the pediatric PAINT study (NCT00799864), and the adult ECHO (NCT00540449) and THRIVE (NCT00543725) studies (Methods, Supplemental Digital Content 2, https://links.lww.com/INF/G330), described an increase in RPV exposure with decreasing body weight, with allometric scaling exponents of 0.75 for apparent clearance (CL/F) and intercompartmental clearance between central and peripheral compartments (Q/F) and 1 for apparent volume of distribution (Vd/F). The popPK-estimated geometric mean AUC_{24h} was above the minimum target of 80% of the popPK-derived adult geometric mean AUC_{24h}, corresponding to 1666 ng.h/mL at the recommended doses for body weight ranging from 10 to 70 kg.[15]

Safety and Tolerability

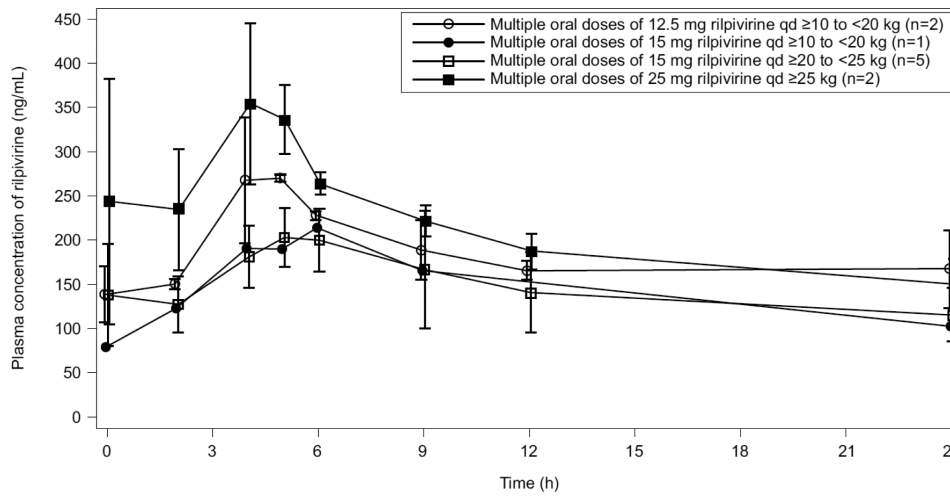
Overall, 19 (73.1%) participants experienced at least 1 AE during the 48-week treatment period (Table 3). The most frequently reported AEs were vomiting [4/26 (15.4%)] and increased alanine aminotransferase [ALT; 3/26 (11.3%); Table 4]. Three participants (11.5%) had an AE that the investigator considered to be at least possibly related to RPV: vomiting (n = 1), abdominal pain (n = 1) and nausea, vomiting, cortisol decreased and folate deficiency (n = 1, all in the same participant).

All AEs were either grade 1 or 2 in severity. No deaths, serious AEs, AEs ≥grade 3 or AEs leading to discontinuation of study medication were reported. AEs of interest were reported in 11/26 (42.3%) participants, with elevated ALT being the most common, reported in 3/26 (11.5%) participants, and headache and increased aspartate aminotransferase each reported in 2/26 (7.7%) participants. All AEs of interest were grade 1 or 2, and none were attributed to RPV.

TABLE 1. Baseline Demographics and Disease Characteristics (Full Analysis Set)

	RPV 12.5 mg qd <20 kg	RPV 15 mg qd <20 kg	RPV 15 mg qd ≥20 to <25 kg	RPV 25 mg qd ≥25 kg	All Participants
N	1	2	5	18	26
Sex, n (%)					
Male	0	2 (100.0)	2 (40.0)	12 (66.7)	16 (61.5)
Female	1 (100.0)	0	3 (60.0)	6 (33.3)	10 (38.5)
Age at screening (years), mean (SD)	5.9 (-)	7.3 (0.47)	8.5 (1.82)	10.3 (1.34)	9.5 (1.83)
Age (years) (categorical), n (%)					
2 to <6 years	1 (100.0)	0	0	0	1 (3.8)
6 to <9 years	0	2 (100.0)	3 (60.0)	3 (16.7)	8 (30.8)
9 to <12 years	0	0	2 (40.0)	15 (83.3)	17 (65.4)
Race, n (%)					
Asian	0	1 (50.0)	1 (20.0)	5 (27.8)	7 (26.9)
Black African American	0	1 (50.0)	4 (80.0)	8 (44.4)	13 (50.0)
White	1 (100.0)	0	0	5 (27.8)	6 (23.1)
Height (cm), mean (SD)	110.8 (-)	112.9 (0.8)	127.0 (4.6)	138.2 (8.3)	133.0 (11.4)
Weight (kg), mean (SD)	17.5 (-)	17.8 (2.2)	23.4 (0.9)	34.9 (8.7)	30.7 (9.8)
BMI (kg/m^2), mean (SD)	14.3 (-)	13.9 (1.6)	14.5 (0.9)	18.1 (3.1)	17.0 (3.1)
HIV-1 RNA, n (%)					
≥50 copies/mL	0	0	1 (20.0)	0	1 (3.8)
<50 copies/mL	1 (100.0)	2 (100.0)	4 (80.0)	18 (100.0)	25 (96.2)
CD4+ count (cells/mm^3), mean (SD)	947.0 (-)	1009.0 (189.5)	722.6 (165.8)	897.9 (249.4)	874.7 (234.1)
≥350 to <500 cells/mm^3, n (%)	0	0	1 (20.0)	1 (5.6)	2 (7.7)
≥500 to <750 cells/mm^3, n (%)	0	0	1 (20.0)	6 (33.3)	7 (26.9)
≥750 cells/mm^3, n (%)	1 (100.0)	2 (100.0)	3 (60.0)	11 (61.1)	17 (65.4)
Duration of HIV infection (years), mean (SD)	5.5 (-)	6.7 (1.2)	4.9 (1.9)	8.4 (2.8)	7.5 (2.9)
Total patient years of RPV exposure	0.9	1.9	4.6	16.8	24.2

BMI indicates body mass index; RPV, rilpivirine; SD, standard deviation.



conc.; concentration; h, hour; qd, once-daily; SD, standard deviation

FIGURE 1. Mean (SD) plasma concentration-time profile of rilpivirine. conc. indicates concentration; h, hour; qd, once-daily; SD, standard deviation.

All Fridericia-corrected QT interval (QTcF) values were normal (<460 ms) for all participants at all timepoints. At visits where both predose and 4-hours postdose electrocardiograms were available (day 1/baseline and week 4 intensive PK visit), only small variations with no change >60 ms in QTcF interval 4 hours postdose were observed compared with the predose value.

Three (11.5%) participants had grade 3 laboratory abnormalities [decreased neutrophils and precursors (n = 1); estimated glomerular filtration rate based on a >30% decrease from baseline (n = 2; normal absolute estimated glomerular filtration rate values at all available timepoints in both participants)]. No clinically meaningful changes in laboratory values, vital signs measurements, physical examination assessments (including growth and pubertal development assessed by Tanner staging), or other safety-related observations were reported up to week 48.

Antiviral Activity

At both week 24 and week 48, all participants remained virologically suppressed (plasma HIV-1 RNA <50 copies/mL). At week 48, the mean (SE) change in CD4 count from baseline was –8.4 (29.72) cells/μL and the mean (SE) increase in the proportion of CD4 cells to all lymphocytes was 0.9% (1.12%).

Retrospective antiretroviral archived resistance data from 18/26 (69.2%) participants at screening were obtained. At

TABLE 2. Pharmacokinetic Results (Intensive PK assessment) After Multiple Oral Administrations of Rilpivirine at 12.5, 15 and 25 mg Once-Daily (PK Analysis Set)

PK of RPV, Mean (SD), t_{max}: Median (Range)[a]	RPV 12.5 mg qd ≥10 to <20 kg	RPV 15 mg qd ≥10 to <20 kg	RPV 15 mg qd ≥20 to <25 kg	RPV 25 mg qd ≥25 kg
n	2	1	5[b]	2[c]
C_{0h} (ng/mL)	116; 161	79.3	138 (58.7)	146; 342
C_{24h} (ng/mL)	137; 199	103	115 (30.5)	129; 170
C_{min} (ng/mL)	116; 137	79.3	110 (32.9)	129; 170
C_{max} (ng/mL)	273; 318	214	217 (43.1)	309; 418
$C_{ss,av}$ (ng/mL)	172; 194	145	146 (39.1)	188; 235
t_{max} (h)	4.00; 5.00	6.05	5.08 (5.00–9.00)	4.03; 5.03
AUC_{24h} (ng.h/mL)	4116; 4646	3494	3506 (946)	4514; 5644
CL/F (L/h)	2.69; 3.04	4.29	4.49 (0.983)	4.43; 5.54
V_{ss}/F (L)	-	-	154; 234	184
FI (%)	79.3; 104	92.6	75.4 (15.9)	95.7; 105

AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours postdose; C_{0h}, predose plasma concentration; C_{24h}, plasma concentration at 24 hours postdose; CL/F, total apparent clearance at steady-state; C_{max}, maximum observed plasma concentration; C_{min}, minimum observed plasma concentration; $C_{ss,av}$, average plasma concentration at steady-state; FI, fluctuation index; PK, pharmacokinetics; qd, once-daily; RPV, rilpivirine; t_{max}, time to reach the maximum observed plasma concentration; V_{ss}/F (L), apparent volume of distribution at steady-state.

aIndividual values are shown for n <3.

bn = 2 for V_{ss}/F.

cn = 1 for V_{ss}/F.

TABLE 3. Overall Summary of Adverse Events by Weight Groups (Full Analysis Set)

	RPV 12.5 mg qd <20 kg	RPV 15 mg qd <20 kg	RPV 15 mg qd ≥20 to <25 kg	RPV 25 mg qd ≥25 kg	All Participants
Participants, n (%)	1	2	5	18	26
≥1 AE	1 (100.0)	0	5 (100.0)	13 (72.2)	19 (73.1)
≥1 serious AE	0	0	0	0	0
Death due to AE	0	0	0	0	0
DAIDS grade 1 AE (mild)	1 (100.0)	0	3 (60.0)	13 (72.2)	17 (65.4)
DAIDS grade 2 AE (moderate)	1 (100.0)	0	4 (80.0)	3 (16.7)	8 (30.8)
DAIDS grade 3 AE (severe)	0	0	0	0	0
DAIDS grade 4 AE (potentially life-threatening)	0	0	0	0	0
AE possibly related to RPV	0	0	0	1 (5.6)	1 (3.8)
AE probably related to RPV	0	0	0	0	0
AE very likely related to RPV	1 (100.0)	0	0	1 (5.6)	2 (7.7)
AE related to RPV	1 (100.0)	0	0	2 (11.1)	3 (11.5)
Serious AE related to RPV	0	0	0	0	0
AE possibly related to background regimen	0	0	0	1 (5.6)	1 (3.8)
AE probably related to background regimen	0	0	0	0	0
AE very likely related to background regimen	1 (100.0)	0	0	0	1 (3.8)
AE related to background regimen	1 (100.0)	0	0	1 (5.6)	2 (7.7)
Serious AE related to background regimen	0	0	0	0	0

All AEs reported in this table were grade 1 or 2; Rilpivirine dose group was determined by the initial administered dose, irrespective of subsequent dose-alterations; No participants in the 15 mg qd, <20 kg and 25 mg qd, 20 to <25 kg weight group.

AE indicates adverse event; DAIDS, Division of AIDS; RPV, rilpivirine.

screening, 4, 3 and 4 participants each carried at least one archived RPV-, NRTI- and INSTI-resistance-associated mutation (RAM), respectively (Table, Supplemental Digital Content 6, https://links.lww.com/INF/G330). In addition, at least 1 PI RAM was detected in all participants with data, and at least 1 primary PI RAM was detected in 2 participants (IAS-USA list 2019; data not shown). Despite these preexisting RAMs, all participants remained virologically suppressed at week 48.

Pharmacokinetic-pharmacodynamic Relationships

As all participants were virologically suppressed at week 48 (plasma HIV-1 RNA <50 copies/mL), a relation between PK and antiviral activity parameters of interest could not be established. Within the simulated RPV exposure range from the popPK analysis, no clear relationship was observed between RPV PK and any of the safety parameters of interest (including QTcF abnormalities and ALT) in this relatively small cohort of participants.

Treatment Adherence

Based on pill count, the mean (SD) RPV treatment adherence at week 24 was 97.2% (6.0%). At week 48, the mean (SD) RPV treatment adherence was 98.9% (2.9%), with 91.3% of participants demonstrating >95% adherence to RPV treatment. Based on the questionnaires, 24/26 (92.3%) participants never missed an RPV dose or background regimen in the last 3 days before a study visit up to week 48.

Patient Reported Outcomes

The palatability questionnaire responses were available from all 8 participants who took the 2.5-mg tablets (12.5 mg dose: n = 1; 15 mg dose: n = 7). Most respondents rated the taste of 2.5-mg tablets dispersed in water as "really good" [n = 6 (75%)], while one respondent each (12.5%) rated it as "okay" or "pretty good ".

Fifteen of the 19 participants who took the 25-mg tablet (including 1 participant who switched from 15 to 25 mg due to

TABLE 4. Treatment-emergent Adverse Events by System Organ Class in at Least 5% of Participants (Full Analysis Set)

	≥2 to <6 Years (n = 1)	≥6 to <12 Years (n = 25)	All Participants (N = 26)
Participants, n (%)			
Gastrointestinal disorders	1 (100.0)	7 (28.0)	8 (30.8)
Vomiting	1 (100.0)	3 (12.0)	4 (15.4)
Abdominal pain	0	2 (8.0)	2 (7.7)
Nausea	0	2 (8.0)	2 (7.7)
Infections and infestations	1 (100.0)	6 (24.0)	7 (26.9)
Rhinitis	1 (100.0)	1 (4.0)	2 (7.7)
Upper respiratory tract infection	0	2 (8.0)	2 (7.7)
Investigations	1 (100.0)	5 (20.0)	6 (23.1)
ALT increased	0	3 (12.0)	3 (11.5)
AST increased	0	2 (8.0)	2 (7.7)
Nervous system disorders	0	5 (20.0)	5 (19.2)
Headache	0	2 (8.0)	2 (7.7)
Respiratory, thoracic and mediastinal disorder	0	4 (16.0)	4 (15.4)
Nasal congestion	0	2 (8.0)	2 (7.7)
General disorders and administration site conditions	1 (100.0)	2 (8.0)	3 (11.5)
Pyrexia	1 (100.0)	1 (4.0)	2 (7.7)
Metabolism and nutrition disorders	0	3 (12.0)	3 (11.5)
Decreased appetite	0	2 (8.0)	2 (7.7)

All AEs reported in this table were grade 1 or 2.
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

weight increase) provided responses to the swallowability questionnaire. Most respondents [n = 14 (93.3%)] found the tablet(s) easy to swallow and one (6.7%) responded that it was difficult to swallow. When rating long-term daily use, 11 (73.3%) respondents found it "good to take," 3 (20.0%) found it "acceptable" and 1 (6.7%) found it "unacceptable ".

DISCUSSION

In this phase-2 PICTURE study in children (ages ≥2 to <12 years) with virologic suppression at baseline, RPV PK exposure targets were met, the safety profile was consistent with previous studies of RPV, and virological suppression was maintained throughout the 48 weeks of the study.

RPV absorption was generally rapid, with the mean peak plasma concentrations typically achieved within 4–6 hours after dosing. RPV exposures were similar to or slightly higher than exposures in adults at the recommended doses for the respective weight bands.[15,19] Despite the slightly higher exposures, safety findings in this study were consistent with the established safety profile of RPV in adults and adolescents, and no new safety concerns were reported. All reported AEs were not serious, were grade 1 or 2 in severity, and no abnormalities in QTcF intervals were observed. In a study with dolutegravir as first- or second-line treatment in children who weighed ≥14 kg, both AEs grade ≥3 and serious AEs were reported in 20.9% and 10.0% of participants, respectively, albeit this was a much larger study in children who were not virologically suppressed.[20] Additionally, within the observed RPV exposure range, no clear relationship was observed between RPV PK and the safety parameters of interest.

In the present study, all participants were virologically suppressed at baseline (plasma HIV-1 RNA <50 copies/mL), and this status was maintained up to week 48, demonstrating durable antiviral activity of an RPV-based regimen in this pediatric population. All participants maintained a high CD4 count throughout the study. Virologic failure can also be associated with the presence of preexisting drug resistance or suboptimal adherence. Although preexisting RAMs were observed in a notable proportion of participants, all participants successfully maintained virologic suppression at week 48. Moreover, a high level of treatment adherence was noted in this study, with all participants demonstrating >95% adherence to RPV.

Approximately 75% of the participants rated the palatability of the RPV 2.5-mg tablets dispersed in water and the swallowability of the RPV 25-mg tablets as "really good" or "good." In this pediatric population, acceptable palatability and swallowability are crucial factors in promoting optimal treatment adherence.

Dolutegravir-based regimens are now the preferred first-line ARV therapy for children. Although RPV is not included in the WHO or US guidelines for the use of ARV agents in pediatric HIV infection, it could be a valuable ARV therapy option when an NNRTI is considered for developing an appropriate treatment regimen for children aged ≤12 years. Ongoing studies are evaluating oral RPV with an integrase inhibitor (dolutegravir[21] or cabotegravir[22]) in virologically suppressed children ≤12 years of age.

A limitation of the study is that it is a small, single-arm, open-label study. Therefore, the appropriateness of weight-based dosing was evaluated using a popPK model approach, combining PK data from the current PICTURE study with PK data from the pediatric PAINT study (NCT00799864),[18] and the adult ECHO (NCT00540449) and THRIVE (NCT00543725) studies.

In summary, in this study of oral RPV in combination with background ART in children aged ≥2 to <12 years with virologic suppression, RPV exposure was within the target range for all doses, with no new safety concerns and a high level of adherence. At week 48, the results indicate that oral RPV can help maintain virologic suppression (HIV-1 RNA <50 copies/mL) in the studied population living with HIV-1.

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REFERENCES

1. World Health Organization. Global HIV Programme: treatment and care in children and adolescents. Available at: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/

treatment-and-care-in-children-and-adolescents. Accessed 23 November, 2024.

2. UNAIDS. Global HIV & AIDS statistics—fact sheet. UNAIDS. Available at: https://www.unaids.org/en/resources/fact-sheet. Accessed 10 November, 2024.
3. Waalewijn H, Turkova A, Rakhmanina N, et al; Pediatric Antiretroviral Working Group (PAWG). Optimizing pediatric dosing recommendations and treatment management of antiretroviral drugs using therapeutic drug monitoring data in children living with HIV. *Ther Drug Monit*. 2019;41:431–443.
4. Han WM, Law MG, Egger M, et al; IeDEA collaboration. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries. *Lancet HIV*. 2021;8:e766–e775.
5. Lutz B. Neurobiology of cannabinoid receptor signaling. *Dialogues Clin Neurosci*. 2020;22:207–222.
6. Penazzato M, Townsend CL, Rakhmanina N, et al; PADO4 participants. Prioritising the most needed paediatric antiretroviral formulations: the PADO4 list. *Lancet HIV*. 2019;6:e623–e631.
7. WHO Guidelines Approved by the Guidelines Review Committee. *Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV*. Geneva: World Health Organization Copyright © World Health Organization 2015; 2015.
8. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available at: https://www.who.int/publications/i/item/WHO-CDS-HIV-18.51. Accessed 23 November, 2024.
9. 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. 2024. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed 26 May 2025, 2025.
10. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis*. 2006;43:939–941.
11. Pasternak AO, Vroom J, Kootstra NA, et al; Co-morBidity in Relation to Aids (COBRA) Collaboration. Non-nucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy is associated with lower cell-associated HIV RNA and DNA levels compared to protease inhibitor-based therapy. *eLife*. 2021;10:e68174.
12. Weiser SD, Guzman D, Riley ED, et al. Higher rates of viral suppression with nonnucleoside reverse transcriptase inhibitors compared to single protease inhibitors are not explained by better adherence. *HIV Clin Trials*. 2004;5:278–287.
13. Cohen CJ, Molina JM, Cahn P, et al; ECHO Study Group. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr (1999)*. 2012;60:33–42.
14. Penazzato M, Giaquinto C. Role of non-nucleoside reverse transcriptase inhibitors in treating HIV-infected children. *Drugs*. 2011;71:2131–2149.
15. Lombaard J, Bunupuradah T, Flynn PM, et al. Rilpivirine as a treatment for HIV-infected antiretroviral-naïve adolescents: week 48 safety, efficacy, virology and pharmacokinetics. *Pediatr Infect Dis J*. 2016;35:1215–1221.
16. Pertwee RG. Elevating endocannabinoid levels: pharmacological strategies and potential therapeutic applications. *Proc Nutr Soc*. 2014;73:96–105.
17. EDURANT (rilpivirine) highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202022s000lbl.pdf. Accessed 23 November, 2024.
18. Lombaard J, Moolasart V, Lutaakome J, et al. Pharmacokinetics, safety and antiviral activity of rilpivirine in antiretroviral-naïve children with HIV ≥6 to <12 years old: week 48 and final analysis of cohort 2 from the open-label, phase 2 PAINT study. *Pediatr Infect Dis J*. 2025;44:657–664.
19. Jantarabenjakul W, Anugulruengkitt S, Kasipong N, et al; HIVNAT 220 study. Pharmacokinetics of rilpivirine and 24-week outcomes after switching from efavirenz in virologically suppressed HIV-1-infected adolescents. *Antivir Ther*. 2018;23:259–265.
20. Turkova A, White E, Mujuru HA, et al; ODYSSEY Trial Team. Dolutegravir as first- or second-line treatment for HIV-1 infection in children. *N Engl J Med*. 2021;385:2531–2543.
21. Hill MN, Kumar SA, Filipski SB, et al. Disruption of fatty acid amide hydrolase activity prevents the effects of chronic stress on anxiety and amygdalar microstructure. *Mol Psychiatry*. 2013;18:1125–1135.
22. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. *Physiol Rev*. 2003;83:1017–1066.