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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

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Background: Rilpivirine has shown adequate antiviral activity, consistent pharmacokinetics and safety in adults and adolescents living with HIV-1. Pharmacokinetics, safety, and antiviral activity of rilpivirine were assessed in children, following at least 48 weeks of treatment.

Methods: Cohort 2 of the open-label, phase 2 PAINT study (NCT00799864) included antiretroviral-naïve children living with HIV-1 ≥6 to <12 years old, with a viral load ≤100,000 RNA copies/mL. Participants received weight-based doses of rilpivirine in combination with a background regimen containing 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs).

Results: Of the 18 children enrolled, 17 completed the 48-week treatment period. Participants were mostly boys (61%), median (range) age of 9.0 years (6–11 years) and weight of 25.0 kg (17–51 kg). Most children [14/18 (78%)] were adherent (>95%) to the treatment. Pharmacokinetic exposures were similar across the recommended weight-based doses and within a range comparable to exposures seen in adult studies. At week 48, 13/18 (72%) children achieved virologic response (HIV-1 RNA <50 copies/mL, FDA Snapshot). The mean (SE) increase from baseline to week 48 in CD4+ count was 213.4 (77.80) cells/μL. Overall postbaseline, 2 participants experienced virologic failure, of which 1 carried treatment-emergent rilpivirine resistance-associated mutations (RAMs); 3 of 5 participants with suspected virologic failure carried rilpivirine and NRTI RAMs. No new safety signals were identified in this population.

Conclusions: At week 48, rilpivirine achieved adequate viral suppression in antiretroviral-naïve children ≥6 to <12 years of age. The pharmacokinetic, safety and virologic profile of rilpivirine in this age group was consistent with observations in adults and adolescents living with HIV-1.

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

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Although global HIV rates have been declining, 1.5 million children <15 years of age were living with the disease in 2022 and HIV continues to pose a significant public health threat, especially in highly endemic regions.[1–3] High rates of virologic failure (VF) and inadequate response to antiretroviral (ARV) therapies in the pediatric population present unique challenges in treating HIV-1 and these are often linked to suboptimal adherence as children rely on parents or caregivers or may simply refuse to take medications.[4–11] More recent therapies such as integrase strand transfer inhibitors are recommended in both ARV-naïve and treatment-experienced children; however, challenges related to adherence, including factors such as pill size and pill burden remain.[12] Thus, there still exists a need for age-appropriate therapies with weight-specific dosing options to optimize long-term treatment outcomes in children and adolescents living with HIV.

Rilpivirine, a nonnucleoside reverse transcriptase inhibitor (NNRTI) taken as a 25-mg tablet once daily (qd) in combination with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), has demonstrated noninferior efficacy to efavirenz in treatment-naïve adults living with HIV-1.[13–16] Pharmacokinetics (PK), safety and antiviral activity of rilpivirine plus 2 NRTIs in ARV-naïve children and adolescents ≥6 to <18-years old with HIV-1 were assessed in an open-label, multicenter, phase 2 study (PAINT study; NCT0079986).

In Cohort 1 of the PAINT study (adolescents ≥12 to <18 years old), the PK, safety and antiviral activity of rilpivirine in treatment-naïve adolescents with HIV-1 were comparable to findings in adults.[17] Rilpivirine exhibited acceptable long-term safety and viral suppression in the Cohort 1 postweek 48 treatment extension period (up to 240 weeks), which also illustrated the significance of optimal adherence (associated with higher virologic response) in adolescents living with HIV-1.[18]

Described here are the PK, safety and antiviral activity of rilpivirine in ARV-naïve children ≥6 to <12-years of age (Cohort 2) in the 48-week initial treatment period and the safety and antiviral activity in the postweek 48 extension period.

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The data sharing policy 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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METHODS

Study Design and Participants

Cohort 2 of the PAINT study included ARV-naïve children ≥6 to <12 years old with HIV-1 infection and was conducted across 4 sites in South Africa, Thailand and Uganda. The study comprised a maximum screening period of 8 weeks, initial treatment period of 48 weeks and a postweek 48 treatment extension period of 4 years (which was removed during the conduct of the study). After completion of the PAINT study, the participants could continue receiving treatment in the roll-over study TMC278IFD3004 (NCT02494986) (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/G180). We report the final analysis of Cohort 2 after at least 48 weeks of treatment or early discontinuation.

Cohort 2 included children weighing ≥17 kg, with documented HIV-1 infection, plasma viral load ≥500 and ≤100,000 HIV RNA copies/mL at screening, genotypic evidence of sensitivity to NRTIs and NNRTIs, and no previous treatment with an HIV vaccine or drug (exception: single dose of nevirapine or up to 6 weeks of zidovudine for prevention of vertical transmission). Participants with a positive HLA-B*5701 test at screening, currently active (not clinically stabilized for ≥30 days) AIDS-defining illness (Centers for Disease Control and Prevention Category-C conditions), known or suspected acute HIV-1 infection and risk factors for corrected QT interval (QTc) prolongation were excluded.

The study was conducted in accordance with the Declaration of Helsinki, consistent with good clinical practices and the applicable regulatory requirements. The protocol and amendments were approved by local ethics committees. Written informed consent was obtained from participants and their legally acceptable representatives before enrollment.

Treatment

Based on all accumulating rilpivirine data, and upon the Independent Data Monitoring Committee (IDMC) recommendations, rilpivirine doses evolved during the PAINT 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). Before the analyses, which led to the introduction of weight-based dosing, 5 children with a body weight ≥20 to <25 kg were started on the 25-mg dose. For the weight-adjusted doses (12.5 and 15 mg), 2.5 mg tablets of rilpivirine were dispersed in water before administration. Rilpivirine was administered with a meal in combination with an investigator-selected background regimen consisting of 2 NRTIs (zidovudine, abacavir, or tenofovir disoproxil fumarate in combination with either lamivudine or emtricitabine). The choice of background therapy was based on the local standard of care treatment for children ≥6 to <12 years old and given as coformulation or as separate components according to local availability and use in the country. At the visit for intensive PK sampling, participants received rilpivirine with a standardized breakfast. Participants could choose to take rilpivirine at another time of day (always with a meal) after the visit of the intensive PK sampling.

Pharmacokinetics

PK parameters (primary endpoints) at steady state were calculated using noncompartmental analysis based on intensive PK samples collected after ≥2 weeks of study treatment (timepoints: predose, 0-, 2-, 4-, 5-, 6-, 9-, 12- and 24-hour postdose). Sparse PK samples were collected at any time during the visits at weeks 4, 8, 12, 24 and 48. Plasma concentrations were measured using a validated liquid chromatography with tandem mass spectrometry method with a lower limit of quantification of 1 ng/mL. Intensive and sparse PK data of the pediatric studies [PAINT study: Cohort 1/2 and TMC278HTX2002/PICTURE study (NCT04012931)] and intensive PK data of adult studies [TMC278-C209/ECHO (NCT00540449) and TMC278-C215/THRIVE (NCT00543725)] were used to build a population PK (PopPK) model.

Adherence

Adherence during the 48-week treatment period and until the study end was assessed based on drug accountability using pill count, the Study Adherence Questionnaire for Children and Teenagers, and the Study Adherence Questionnaire for Caregivers.

Safety

Safety and tolerability were assessed at each visit. Safety assessments included adverse events (AEs), clinical laboratory parameters, vital signs, and physical examination. AEs and clinical laboratory abnormalities were graded according to the Division of AIDS severity table.[19]

Antiviral Activity and Virology Analysis

Secondary endpoints included assessment of antiviral activity (FDA Snapshot algorithm[20]), change from baseline in CD4+ cell count and HIV drug resistance determination. Plasma viral load and $CD4^+$ cell counts were measured at screening, baseline, week 2, every 4 weeks from week 4 until week 16, and every 8 weeks thereafter.

HIV-1 genotypes were analyzed for resistance-associated mutations (RAMs) in protease (according to International Antiviral Society–USA) and reverse transcriptase.[21] Resistance analysis included real-time plasma-based standard genotypic and phenotypic analysis (PhenoSense assay; Monogram Biosciences) at baseline, screening, week 24, week 48, postweek 48 and early withdrawal, and at any other visit in case of suspected VF (SVF). Peripheral blood mononuclear cell (PBMC)-based proviral DNA sequencing and plasma-based genotypic next-generation deep sequencing were also performed (Supplemental Digital Content 2, http://links.lww.com/INF/G181).

A confirmed responder was defined as having 2 consecutive plasma HIV-1 RNA measurements of <50 copies/mL. SVF was defined as plasma HIV-1 RNA ≥200 copies/mL after confirmed plasma HIV-1 RNA of <50 copies/mL. VF was defined as lack of response, characterized by a decrease from baseline of <1.0 $\log_{10}$ in plasma viral load at week 12; or loss of response, defined as 2 consecutive plasma HIV-1 RNA measurements of ≥400 copies/mL after having been confirmed virologic responder (also meets SVF criteria).

Statistical Analysis

No formal sample size calculation was performed. Approximately 40 participants were planned to be enrolled collectively in the PAINT Cohort 2 and the PICTURE study (children ≥2 to <12 years of age) based on regulatory requirements. This sample size was considered adequate to draw conclusions on the steady-state exposure of rilpivirine in this group of children. An Independent IDMC was appointed to monitor PK, antiviral activity, and safety/tolerability data and make recommendations regarding rilpivirine treatment continuation, modification, dose adjustments, or termination of the study.

All participants receiving at least one dose of rilpivirine were included in the full analysis set that was the primary population for all analyses. The dose groups included in the analysis were the recommended weight-based once-daily doses of 12.5 mg (<20 kg), 15 mg (≥20 to <25 kg), 25 mg (≥25 kg), and a higher dose of 25 mg (≥20 to <25 kg), which was initiated before the introduction of weight-based dosing in the study. For the intensive PK data, descriptive statistics were calculated for the plasma concentrations

of rilpivirine at each timepoint and for the derived PK parameters. Antiviral activity and safety results were summarized descriptively. $CD4^+$ cell count was analyzed based on observed values.

RESULTS

Patient Disposition

Cohort 2 of the PAINT study was conducted between May 26, 2016, and August 16, 2022. In total, 38 children were screened and 18 were enrolled [12.5 mg qd (<20 kg), n = 2; 15 mg qd (≥20 to <25 kg), n = 2; 25 mg qd (≥20 to <25 kg), n = 5; 25 mg qd (≥25 kg), n = 9]. The 5 children with a body weight ≥20 to <25 kg who were started on the 25-mg, once-daily dose continued the study on the same 25 mg, once-daily dose as per IDMC review of the PK, safety and efficacy of these first 5 children enrolled in Cohort 2. Overall, 2 participants switched from 15 to 25 mg qd due to weight change; 1 of these 2 participants had this dose adjustment at the time of roll-over into study TMC278IFD3004. The most common reasons for screening failure (n = 20) were plasma HIV RNA ≥100,000 copies/mL (n = 11) and NNRTI resistance (n = 8). Of the 18 enrolled participants, 17 completed the 48-week treatment period; 1 participant prematurely discontinued the study after reaching a virologic endpoint.

Demographics and Baseline Characteristics

Demographic characteristics (except age and body weight) were generally comparable across the dose-weight groups (Table 1). Most children were boys (61%), the median age was 9 years (range: 6–11 years) and median weight was 25 kg (range: 17–51 kg). All participants were ARV-naïve with a median duration of known HIV-1 infection of 1.2 months (range: 0–72 months). The median baseline plasma viral load was 55,400 (range: 567–149,000) copies/mL; 4/18 (22%) participants had a baseline plasma viral load of >100,000 copies/mL but remained eligible since the screening HIV-1 RNA was ≤100,000 copies/mL. Median baseline $CD4^+$ cell count was 432.5 (range: 12–2068) cells/mm^3. At baseline, lamivudine in combination with abacavir [10/18 (56%); 40–100% per dose-weight group] was the most common NRTI backbone.

Pharmacokinetics

A total of 195 PK samples (intensive and sparse sampling) were available for Cohort 2 of the PAINT study. Intensive PK data obtained after multiple oral once-daily dosing of rilpivirine at 12.5, 15 or 25 mg are summarized in Figure 1, and individual profiles for each dose-weight group are provided in Figure, Supplemental Digital Content 3, http://links.lww.com/INF/G182. Mean maximum plasma concentrations (C_{max}) were reached at 4–6 hours postdose. Steady-state C_{max} and area under-the-concentration-time curve from 0 to 24 hours (AUC_{24h}) were similar at recommended once-daily doses of 25 mg (≥25 kg), 15 mg (≥20 to <25 kg) and 12.5 mg (<20 kg) and slightly higher at 25 mg (≥20 to <25 kg). PopPK analysis indicated that exposures increased with decreasing bodyweight, 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). At the recommended doses, the PopPK-estimated geometric mean AUC_{24h} was above 80% of the adult geometric mean AUC_{24h} of 1666 ng.h/mL for body weights ranging from 10 to 70 kg (data on file).

Exposure and Adherence

The mean [standard deviation (SD)] duration of rilpivirine exposure across all 18 participants during the 48-week period was 48.3 (3.74) weeks with a total of 16.67 patient-years. The mean (SD) exposure to the study end was 100.2 (63.26) weeks with a total of 34.57 patient-years.

The mean (SD) rilpivirine treatment adherence (based on pill count) for all participants through week 48 was 98.3% (6.9) and 98.4% (6.0) through the end-of-study (Table, Supplemental Digital Content 4, http://links.lww.com/INF/G183); majority of participants [14/18 (78%)] were adherent (adherence level >95%) to rilpivirine treatment during the study.

Additional results for taste acceptability and palatability are described in Supplemental Digital Content 5, http://links.lww.com/INF/G184.

Safety and Tolerability

Overall, 17/18 (94%) participants experienced at least one AE during the 48-week treatment period (Table 2). All AEs were grade 1 or 2 in severity with no reports of serious AEs, AEs leading to drug discontinuation, or deaths during the 48-week period. The most frequent (n ≥ 2) AEs were upper respiratory tract infection [12/18 (67%)], otitis media, decreased appetite, anemia, diarrhea, vomiting, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), cough and rash [2/18 (11%) participants each]. Grade 1 increases in ALT and AST were deemed possibly related to rilpivirine by the investigator and both occurred in the same patient in the 25 mg, once-daily, ≥25 kg dose-weight group during the 48-week treatment period. The AEs resolved spontaneously during the 48-week treatment period. The participant continued receiving rilpivirine and rolled over to study TMC278IFD3004. No other AEs were considered by the investigator as possibly related to rilpivirine.

AEs of special interest (skin, neuropsychiatric, potential QT prolongation-related, hepatic and endocrinology events and AIDS-defining illnesses) were reported in 6/18 (33%) participants in the 48-week treatment period. These included grade 1 events of increased ALT, increased AST, rash [2/18 (11%) participants each], abnormal adrenocorticotropic hormone stimulation test, dermatitis atopic and headache [1/18 (6%) participant each] and grade 2 QTcB (QTc interval according to Bazett's formula) prolongation [1/18 (6%); Supplemental Digital Content 6, http://links.lww.com/INF/G185]. Most laboratory abnormalities were grade 1 with no clinically meaningful changes. Among the 13 participants with low basal cortisol predose on day 1, 11 had normal serum cortisol values after adrenocorticotropic hormone stimulation at baseline and/or during treatment (Supplemental Digital Content 6, http://links.lww.com/INF/G185). QTcF (QTc interval values according to Fridericia's formula) were normal for all participants throughout the study and no increases from baseline in QTcF by >60 msec were reported at any time point during the study. There were no clinically relevant changes in growth and pubertal development (assessed by Tanner staging) apart from expected increases in height and weight and changes in genitalia and breasts in this population.

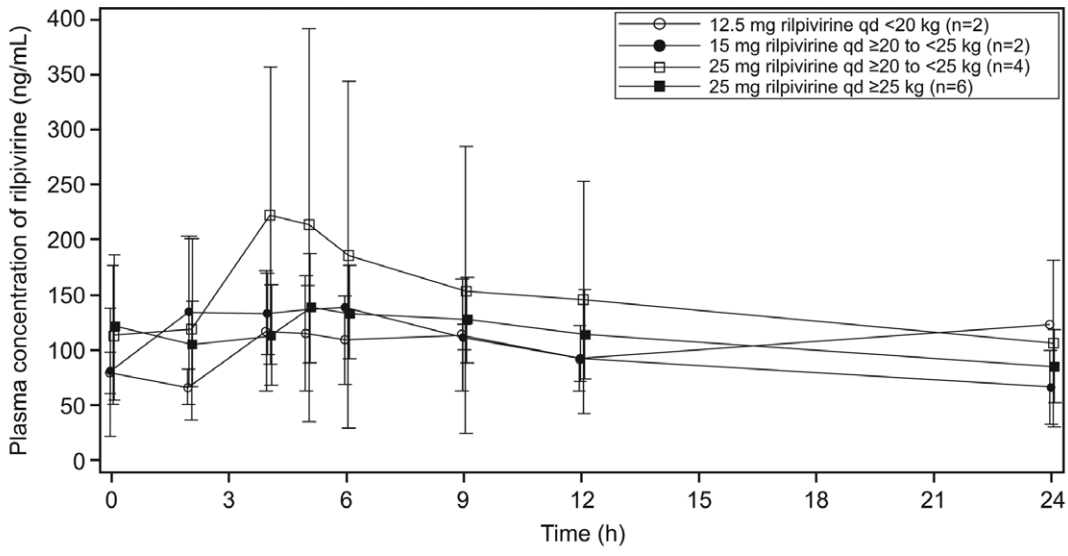
Antiviral Activity

Thirteen of the 18 (72%) participants achieved a virologic response (defined as plasma viral load <50 copies/mL) and 3/18 (17%) had viral load >50 copies/mL at week 48 (Table 3). Two (11%) participants in the 15-mg once-daily (≥20 to ≤25 kg) dose group had missing viral load data at week 48 but remained on the study; latest available viral load was <50 copies/mL in both participants. The mean (SE) change from baseline in plasma viral load was −3.5 (0.32) log_{10} copies/mL at week 48 (Table 2). Individual viral load profiles are shown in Figure, Supplemental Digital Content 7, http://links.lww.com/INF/G186. Of the 4 participants with suboptimal adherence (≤95%), 3 achieved virologic response at week 48 (although viral load was >50 copies/mL as of weeks 60, 72 and 120 for each participant, respectively, and remained >50 copies/mL until study withdrawal) and 1 had VF.

TABLE 1. Demographic and Baseline Characteristics (Full Analysis Set)

	RPV Doses					
	12.5 mg qd, <20 kg	15 mg qd, ≥20 to <25 kg	25 mg qd, ≥20 to <25 kg	25 mg qd, ≥25 kg	All Recommended Doses	All Participants
	n = 2	n = 2	n = 5	n = 9	n = 13	N = 18
Sex, n (%)						
Girls	1 (50)	1 (50)	2 (40)	3 (33)	5 (39)	7 (39)
Boys	1 (50)	1 (50)	3 (60)	6 (67)	8 (62)	11 (61)
Age (years) at screening						
Mean (SD)	6.0 (0.00)	6.5 (0.71)	9.2 (0.84)	9.4 (1.67)	8.5 (2.07)	8.7 (1.81)
Median	6.0	6.5	9.0	10.0	8.0	9.0
6 to <9 years, n (%)	2 (100)	2 (100)	1 (20)	3 (33)	7 (54)	8 (44)
9 to <12 years, n (%)	0	0	4 (80)	6 (67)	6 (46)	10 (56)
Race, n (%)						
Asian	0	0	1 (20)	1 (11)	1 (8)	2 (11)
Black or African American	2 (100)	2 (100)	4 (80)	8 (89)	12 (92)	16 (89)
Country, n (%)						
South Africa	0	0	2 (40)	5 (56)	5 (39)	7 (39)
Thailand	0	0	1 (20)	1 (11)	1 (8)	2 (11)
Uganda	2 (100)	2 (100)	2 (40)	3 (33)	7 (54)	9 (50)
Weight (kg) at baseline						
Mean (SD)	17.0 (0.00)	23.5 (1.06)	23.6 (0.75)	31.4 (8.00)	28.0 (8.67)	26.8 (7.57)
Median	17.0	23.5	24.0	30.0	27.0	25.0
Range	(17; 17)	(23; 24)	(23; 24)	(26; 51)	(17; 51)	(17; 51)
<20 kg, n (%)	2 (100)	0	0	0	2 (15)	2 (11)
20 to < 25 kg, n (%)	0	2 (100)	5 (100)	0	2 (15)	7 (39)
≥25 kg, n (%)	0	0	0	9 (100)	9 (69)	9 (50)
BMI, (kg/m^2) at baseline						
Mean (SD)	14.7 (0.14)	15.3 (1.06)	15.1 (1.50)	16.9 (2.59)	16.3 (2.33)	16.0 (2.17)
Median	14.7	15.3	14.8	16.7	16.0	15.5
Range	(15; 15)	(15; 16)	(14; 18)	(14; 23)	(14; 23)	(14; 23)
HIV-1 subtype, n (%)						
A	1 (50)	0	0	0	1 (8)	1 (6)
A/D	1 (50)	0	0	0	1 (8)	1 (6)
A1	0	2 (100)	0	1 (11)	3 (23)	3 (17)
AE	0	0	1 (20)	1 (11)	1 (8)	2 (11)
C	0	0	2 (40)	5 (56)	5 (39)	7 (39)
Complex	0	0	0	1 (11)	1 (8)	1 (6)
D	0	0	2 (40)	1 (11)	1 (8)	3 (17)
Mode of HIV-1 infection, n (%)						
Mother-to-child transmission	2 (100)	2 (100)	5 (100)	8 (89)	12 (92)	17 (94)
Other	0	0	0	1 (11.1)	1 (7.7)	1 (6)
Clinical stage of HIV-1 infection at screening, n (%)						
Category A (mild symptomatic)	0	1 (50)	2 (40)	3 (33)	4 (31)	6 (33)
Category B (moderately symptomatic)	1 (50)	0	0	2 (22)	3 (23)	3 (17)
Category N (not symptomatic)	1 (50)	1 (50)	3 (60)	4 (44)	6 (46)	9 (50)
HIV-1 viral load (log10 copies/mL) at baseline						
Mean (SD)	5.0 (0.17)	4.3 (0.56)	4.1 (1.04)	4.6 (0.67)	4.6 (0.61)	4.5 (0.76)
Median	5.0	4.3	4.5	4.8	4.8	4.7
Range	(5; 5)	(4; 5)	(3; 5)	(3; 5)	(3; 5)	(3; 5)
HIV-1 viral load (categorical) at baseline, n (%)						
≤100,000 copies/mL	1 (50)	2 (100)	4 (80)	7 (78)	10 (77)	14 (78)
>100,000 copies/mL	1 (50)	0	1 (20)	2 (22)	3 (23)	4 (22)
CD4+ count (cells/mm^3) at baseline						
Mean (SD)	704.5 (218.50)	599.5 (200.11)	612.0 (561.01)	565.8 (615.54)	592.3 (512.39)	597.8 (509.37)
Median	704.5	599.5	407.0	338.0	458.0	432.5
Range	(550; 859)	(458; 741)	(12; 1441)	(107; 2068)	(107; 2068)	(12; 2068)
Background regimen, n (%)						
Individual ARVs	2 (100)	2 (100)	5 (100)	9 (100)	13 (100)	18 (100)
Antivirals for systemic use	2 (100)	2 (100)	5 (100)	9 (100)	13 (100)	18 (100)
Lamivudine	2 (100)	2 (100)	5 (100)	9 (100)	13 (100)	18 (100)
Abacavir	2 (100)	2 (100)	2 (40)	4 (44)	8 (62)	10 (56)
Zidovudine	0	0	2 (40)	4 (44)	4 (31)	6 (33)
Tenofovir disoproxil fumarate	0	0	1 (20)	1 (11)	1 (8)	2 (11)
Combination ARVs	2 (100)	2 (100)	5 (100)	9 (100)	13 (100)	18 (100)
Abacavir + lamivudine	2 (100)	2 (100)	2 (40)	4 (44)	8 (62)	10 (56)
Zidovudine + lamivudine	0	0	2 (40)	4 (44)	4 (31)	6 (33)
Lamivudine + tenofovir disoproxil fumarate	0	0	1 (20)	1 (11)	1 (8)	2 (11)

Recommended doses for rilpivirine 12.5 mg qd for <20 kg, 15 mg qd for 20 to <25 kg and 25 mg qd for ≥25 kg.
BMI indicates body mass index; CD, cluster of differentiation; RPV, rilpivirine; SD, standard deviation.



RPV doses

	12.5 mg qd <20 kg (n = 2[a])	15 mg qd ≥20 to <25 kg (n = 2)	25 mg qd ≥20 to <25 kg (n = 4[b])	25 mg qd ≥25 kg (n = 6[c])
C_{0h}, ng/mL	66.5; 93.8	39.8; 122	115 (63.6)	121 (66.1)
C_{24h}, ng/mL	123; -	43.3; 90.7	52.8; 160	85.5 (33.5)
C_{min}, ng/mL	55.5; 77.9	39.8; 90.7	82.5 (56.3)	73.2 (26.7)
C_{max}, ng/mL	81.9; 156	138; 184	238 (160)	154 (52.2)
$C_{ss,av}$, ng/mL	71.1; 123	80.6; 119	138 (91.1)	111 (35.0)
t_{max}, h	4.07; 6.00	2.00; 6.00	4.50 (3.95–5.00)	2.98 (0.00–9.03)
AUC_{24h}, ng.h/mL	1710; 2958	1933; 2877	3339 (2233)	2610 (776)
CL/F, L/h	4.23; 7.31	5.21; 7.76	11.6 (8.84)	10.3 (3.20)
V_{ss}/F, L	-	139; 307	53.3; 605	300 (142)
FI, %	37.1; 63.5	78.1; 122	113 (57.9)	72.0 (22.8)

FIGURE 1. Mean (SD) plasma concentration-time profiles of rilpivirine after multiple oral dosing per dose-weight category. [a]n = 1 for C_{24h} and n = 0 for V_{ss}/F; [b]n = 2 for C_{24h} and V_{ss}/F; [c]n = 3 for V_{ss}/F. All values expressed as mean (SD). T_{max} expressed as median (range). Individual values are shown for n <3. Recommended doses for rilpivirine are 12.5 mg qd for <20 kg, 15 mg qd for ≥20 to <25 kg, 25 mg qd for ≥25 kg. AUC_{24h} indicates area under concentration-time curve at 24-hour postdose; C_{0h}, C_{24h}, concentration of drug at 0 hour, 24-hour postdose; CL/F, total apparent plasma clearance at steady-state, C_{min}, minimum observed concentration; C_{max}, maximum observed concentration; Css,av, average steady-state plasma concentration; FI, fluctuation index; RPV, rilpivirine; t_{max}, time to C_{max}; V_{ss}/F, absorption-dependent apparent volume of distribution at steady-state.

At week 48, the mean (SE) change from baseline in CD4+ count was 213.4 (77.80) cells/μL (Figure, Supplemental Digital Content 8, http://links.lww.com/INF/G187).

Resistance Analysis

Screening and Baseline Analysis

Standard plasma-based genotypic and phenotypic data were available for all 18 enrolled participants at screening and baseline; NNRTI RAMs were detected in none as per the protocol-defined exclusion criteria. The reverse transcriptase V179I polymorphism (not exclusionary) was detected in 4/18 participants. All 18 participants had phenotypic susceptibility to rilpivirine and the NRTI backbone regimen.

Postbaseline Analysis

In total, 6/18 participants had postbaseline data available for standard plasma-based genotypic testing (Table 4). Of the 6 participants, 2 reported VF, 3 met the SVF criteria only (n = 5 total SVF), and 1 did not meet the SVF criteria but discontinued due to meeting a virologic endpoint (non-SVF); 2 (both SVF) of these 6 observations were reported in the first 48 weeks. Treatment-emergent rilpivirine RAMs (1/2 VF, 3/3 SVF, 1 non-SVF; E138G, E138K, E138Q, H221Y, K101E, M230L and Y181I) were detected in 5 of these 6 participants and treatment-emergent NRTI RAMs (3/3 SVF, 1 non-SVF; K65R, M184I, M184V, M41L, Y115F and V179I) were detected in 4. Two of the 3 participants with SVF at weeks 60 and 72 had suboptimal adherence. Results for PBMC-based proviral DNA and plasma-based deep sequencing are provided in Supplemental Digital Content 2, http://links.lww.com/INF/G181.

DISCUSSION

Findings from the final analyses of Cohort 2 from the PAINT study show that rilpivirine in combination with 2 NRTIs achieved

TABLE 2. Summary of Adverse Events During the 48-week Treatment Period (Full Analysis Set)

	RPV Doses					
	12.5 mg qd, <20 kg	15 mg qd, ≥20 to <25 kg	25 mg qd, ≥20 to <25 kg	25 mg qd, ≥25 kg	All Recommended Doses	All Participants
	n = 2	n = 2	n = 5	n = 9	n = 13	N = 18
Participants with ≥1 AE	2 (100)	2 (100)	5 (100)	8 (89)	12 (92)	17 (94)
Participants with a DAIDS grade 1 or mild AE	2 (100)	2 (100)	5 (100)	6 (67)	10 (77)	15 (83)
Participants with a DAIDS grade 2 or moderate AE	0	0	2 (40)	6 (67)	6 (46)	8 (44)
Participants with an AE related to RPV	0	0	0	1 (11)	1 (8)	1 (6)
Most common (≥2 participants) AEs						
Upper respiratory tract infection	2 (100)	2 (100)	3 (60)	5 (56)	9 (69)	12 (67)
Otitis media	1 (50)	0	1 (20)	0	1 (8)	2 (11)
Decreased appetite	0	0	1 (20)	1 (11)	1 (8)	2 (11)
Anemia	0	1 (50)	1 (20)	0	1 (8)	2 (11)
Diarrhea	0	0	0	2 (22)	2 (15)	2 (11)
Vomiting	0	0	1 (20)	1 (11)	1 (8)	2 (11)
ALT increased	0	0	1 (20)	1 (11)	1 (8)	2 (11)
AST increased	0	0	1 (20)	1 (11)	1 (8)	2 (11)
Cough	1 (50)	0	0	1 (11)	2 (15)	2 (11)
Rash	1 (50)	0	0	1 (11)	2 (15)	2 (11)

All values are expressed as n (%). Recommended doses for rilpivirine 12.5 mg qd for <20 kg, 15 mg qd for ≥20 to <25 kg and 25 mg qd for ≥25 kg.
DAIDS indicates The Division of AIDS; RPV, rilpivirine.

and maintained viral suppression in treatment-naïve children with HIV-1 ≥6 to <12 years old. PK exposures following multiple oral dosing of rilpivirine at the recommended doses were similar across all dose-weight groups and within a range comparable to exposures reported in adult studies.[17,22]

Over the period of 48 weeks, no new clinically relevant safety concerns specific to this population emerged. The rates of laboratory abnormalities and study discontinuations due to AEs were low, consistent with the safety profile of rilpivirine in adults and adolescents. There were no AEs of grade 3/4 severity, no signs of adrenal insufficiency and no disturbances in QTc intervals. Most children had low pretreatment basal cortisol, a common manifestation of endocrine dysfunction observed in children living with HIV before initiating ARV treatment.[23] The cortisol levels in most of these participants were normal after adrenocorticotropic hormone stimulation at baseline and did not worsen during treatment. Furthermore, the absence of notable changes during Tanner staging indicated normal pubertal progression, an important observation in children experiencing growth spurt.

Virologic response of 72% at week 48 was comparable with observations in adolescents from Cohort 1[17] (72%), and in the same range as those observed in ARV-naïve adults[14] (82%) taking the study differences into account. Differences in study design and population characteristics present a challenge in drawing direct comparisons: the adult and adolescent study populations may not be comparable to the Cohort 2 population (children) due to differences in study size and population characteristics [eg, baseline viral load (<100,000 copies/mL), country/race and age]. However, the virologic response rates observed in this study were consistent with the range reported at week 48 in the ODYSSEY study (72.1% in the ARV-naïve cohort; 74.5% in the virologically suppressed cohort), which demonstrated the superior efficacy of dolutegravir-based ARV therapies compared with standard of care in children and adolescents ≥4 weeks to <18 years of age.[24]

An increase in CD4+ cell count reflects restoration of immune function in treatment-naïve children with HIV. The emerging NNRTI/rilpivirine RAMs associated with VF and SVF in this study were E138Q, H211Y and K101E that have been identified previously in studies of rilpivirine in adults and adolescents.[14,17] The deep sequencing results were generally consistent with the results obtained through standard plasma-based or PBMC-based proviral DNA sequencing, suggesting that standard plasma-based sequencing was adequate for the purpose of participant management in this study. The occurrence of resistance among the ARV-naïve children underscores the need for continued adherence.

TABLE 3. Virologic Response Snapshot Outcome (<50 Copies/mL) at Week 48 (Full Analysis Set)

RPV Doses						
Virologic Response	12.5 mg qd, <20 kg	15 mg qd, ≥20 to <25 kg	25 mg qd, ≥20 to <25 kg	25 mg qd, ≥25 kg	All Recommended Dose	All Participants
	n = 2	n = 2	n = 5	n = 9	n = 13	N = 18
HIV-1 RNA <50 copies/mL	1 (50)	0	4 (80)	8 (88.9)	9 (69)	13 (72)
Virologic failure	1 (50)	0	1 (20)	1 (11.1)	2 (15)	3 (17)
HIV-1 RNA ≥50 copies/mL	1 (50)	0	1 (20)	0	1 (8)	2 (11)
Virologic failure—discontinued due to other reason and last available HIV-1 RNA ≥50 copies/mL	0	0	0	1 (11.1)	1 (8)	1 (6)
No viral load data in time window	0	2 (100)	0	0	2 (15)	2 (11)
Missing data during window but on study	0	2 (100)	0	0	2 (15)	2 (11)

All values are n (%). Recommended doses for rilpivirine 12.5 mg qd for <20 kg, 15 mg qd for ≥20 to <25 kg and 25 mg qd for ≥25 kg.
RNA indicates ribonucleic acid; RPV, rilpivirine.

TABLE 4. Postbaseline Plasma-based Standard Resistance Analysis (Full Analysis Set)

	VF	SVF	Not (S)VF	All Participants
	n = 2	n = 5	n = 1	N = 6
At first postbaseline analysis time point, n (%)				
IAS-USA NRTI ≥1	0	3 (60)	1 (100)	4 (67)
K65R	0	0	1 (100)	1 (17)
M184I	0	0	1 (100)	1 (17)
M184V	0	3 (60)	0	3 (50)
M41L	0	1 (20)	0	1 (17)
Y115F	0	0	1 (100)	1 (17)
Extended NNRTI ≥1	1 (50)	4 (80)	1 (100)	5 (83)
E138G	0	1 (20)	0	1 (17)
E138K	0	1 (20)	0	1 (17)
E138Q	1 (50)	2 (40)	0	2 (33)
H221Y	1 (50)	2 (40)	0	2 (33)
K101E	1 (50)	1 (20)	1 (100)	2 (33)
M230L	0	1 (20)	0	1 (17)
V179I	0	1 (20)	0	1 (17)
Y181I	0	0	1 (100)	1 (17)

Rilpivirine RAMs are indicated with bold font.
IAS-USA indicates International Antiviral Society United States of America.

Adherence to rilpivirine treatment was high during the study as captured by pill count. Of the total 6 participants who either discontinued the study due to lack of response and/or were considered SVF, 4 had evidence for lack of adherence (≤95%) by either (or both) week 48 and/or end-of-study; all had drug accountability for rilpivirine among the lowest observed in the study, except 1 who had lack of adherence to background regimen. The study findings illustrate the impact of treatment adherence on the virologic outcomes, highlighting a clear correlation between suboptimal adherence and inadequate virologic suppression in this population.

While ARV therapies are utilized in pediatric practice, there remains a need for newer therapies due to increasing resistance, substantial variations in drug exposure and complexity of available regimens.[25,26] Rilpivirine-based regimens may offer several advantages including adequate viral suppression, stable PK and acceptable tolerability that are key in reinforcing adherence among young patients with HIV initiating a life-long treatment. The World Health Organization Optimal Formulary (2021) is phasing out and no longer recommends efavirenz and NNRTI-based regimens as preferred or alternative options for children, citing increasing NNRTI resistance and suboptimal ARV potency.[25] Dolutegravir-based regimens are now the preferred first-line ARV therapy for children. Although rilpivirine is not included in the World Health Organization or United States guidelines for the use of ARV agents in pediatric HIV infection, it could still be a valuable ARV therapy option when an NNRTI is considered for developing an appropriate treatment regimen for children under 12 years of age.[27]

This open-label study with small sample size included participants from 3 endemic countries for HIV. The study participants were ARV-naïve with a viral load of ≤100,000 copies/mL at the initiation of therapy; therefore, the results may not be generalizable to children with higher viral load or those already receiving therapy. Inferences related to dose-specific effects could not be drawn as the sample size in each dose group was very small, especially in the lower weight groups. Therefore, to assess and determine the appropriateness of the weight-based doses, PK data of the PAINT study were analyzed along with data from the TMC278HTX2002/PICTURE study.

In conclusion, rilpivirine (at weight-based once-daily doses of 12.5, 15 and 25 mg) administered in combination with NRTI background therapy to ARV-naïve children 6–12 years old, achieved exposures within a range comparable to exposures reported in adult studies. The patterns of AEs at week 48 were consistent with patterns reported in studies of adults and adolescents, and no new clinically relevant safety concerns emerged. Treatment with rilpivirine achieved adequate viral suppression at 48 weeks in ARV-naïve children living with HIV-1. Taken together, these PK, safety and antiviral activity results combined with adequate adherence, support the use of oral rilpivirine in ARV-naïve children ≥6 to <12 years old living with HIV-1.

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REFERENCES

1. World Health Organization. Summary of the global HIV epidemic. 2023. Available at: https://www.who.int/images/default-source/departments/hiv/summary-of-the-global-hiv-epidemic-2022.png?sfvrsn=73ac5b6a_13. Accessed August 1, 2023.
2. Alemu GG, Nigussie ZM, Amlak BT, et al. Survival time and predictors of death among HIV infected under five children after initiation of antiretroviral therapy in West Amhara Referral Hospitals, Northwest Ethiopia. *BMC Pediatr*. 2022;22:670.
3. Onyango DO, Akelo V, van der Sande MAB, et al. Causes of death in HIV-infected and HIV-uninfected children aged under-five years in western Kenya. *AIDS*. 2022;36:59–68.
4. Sigaloff KC, Calis JC, Geelen SP, et al. HIV-1-resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor regions: a systematic review. *Lancet Infect Dis*. 2011;11:769–779.
5. van Rossum AM, Fraaij PL, de Groot R. Efficacy of highly active antiretroviral therapy in HIV-1 infected children. *Lancet Infect Dis*. 2002;2:93–102.
6. Walker AS, Doerholt K, Sharland M, et al; Collaborative HIV Paediatric Study (CHIPS) Steering Committee. Response to highly active antiretroviral therapy varies with age: the UK and Ireland Collaborative HIV Paediatric Study. *AIDS*. 2004;18:1915–1924.
7. Castro H, Judd A, Gibb DM, et al; Pursuing Later Treatment Options II (PLATO II) project team for the Collaboration of Observational HIV

Epidemiological Research Europe (COHERE). Risk of triple-class virological failure in children with HIV: a retrospective cohort study. *Lancet*. 2011;377:1580–1587.

8. Chesney MA. Factors affecting adherence to antiretroviral therapy. *Clin Infect Dis*. 2000;30:S171–S176.
9. Mehta K, Ekstrand ML, Heylen E, et al. Adherence to antiretroviral therapy among children living with HIV in South India. *AIDS Behav*. 2016;20:1076–1083.
10. Devendra A, Kohler M, Letsika M, et al. HIV viral suppression in children and adolescents 2 years after transition to dolutegravir: a multicentre cohort study. *AIDS*. 2024;38:1013–1023.
11. Fokam J, Nka AD, Mamgue Dzukam FY, et al. Viral suppression in the era of transition to dolutegravir-based therapy in Cameroon: children at high risk of virological failure due to the lowly transition in pediatrics. *Medicine (Baltimore)*. 2023;102:e33737.
12. Levy ME, Griffith C, Ellenberger N, et al; DC Cohort Executive Committee. Outcomes of integrase inhibitor-based antiretroviral therapy in a clinical cohort of treatment-experienced children, adolescents and young adults with HIV infection. *Pediatr Infect Dis J*. 2020;39:421–428.
13. EDURANT® (rilpivirine). Highlights of prescribing information. 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219016s000lbl.pdf. Accessed November 20, 2024.
14. 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*. 2012;60:33–42.
15. Cohen CJ, Molina JM, Cassetti I, et al; ECHO, THRIVE study groups. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two phase III randomized trials. *AIDS*. 2013;27:939–950.
16. Molina JM, Clumeck N, Redant K, et al; ECHO and THRIVE Study Groups. Rilpivirine vs. efavirenz in HIV-1 patients with baseline viral load 100,000 copies/ml or less: week 48 phase III analysis. *AIDS*. 2013;27:889–897.
17. Lombaard J, Bunupuradah T, Flynn PM, et al. Rilpivirine as a treatment for HIV-infected antiretroviral-naive adolescents: week 48 safety, efficacy, virology and pharmacokinetics. *Pediatr Infect Dis J*. 2016;35:1215–1221.
18. Lombaard J, Ssali F, Thanyawee P, et al. Phase 2 open-label study of long-term safety, tolerability, and antiviral activity of rilpivirine in antiretroviral-naive adolescents living with HIV-1. *Antimicrob Agents Chemother*. 2022;66:e0091621.
19. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse event. Version 2.1. 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed August 3, 2023.
20. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. 2015. Available at: https://www.fda.gov/media/86284/download. Accessed June 09, 2023.
21. Tambuyzer L, Azijn H, Rimsky LT, et al. Compilation and prevalence of mutations associated with resistance to non- nucleoside reverse transcriptase inhibitors. *Antivir Ther*. 2009;14:103–109.
22. 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.
23. Nassoro DD, Mkhoi ML, Sabi I, et al. Adrenal insufficiency: a forgotten diagnosis in HIV/AIDS patients in developing countries. *Int J Endocrinol*. 2019;2019:2342857.
24. 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.
25. World Health Organization. The 2021 optimal formulary and limited-use list for antiretroviral drugs for children: policy brief. 2021. Available at: https://www.who.int/publications/i/item/9789240023529. Accessed August 4, 2023.
26. Lee C, Sapasap J, LaRochelle J, et al. Antiretroviral therapy in children and adolescents: a look into modern single tablet regimens. *J Pediatr Pharmacol Ther*. 2021;26:783–794.
27. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. 2024. Available at: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv. Accessed November 20, 2024.