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Study APV20002: Safety and Efficacy Results Through Week 684 for Pediatric Participants Living with HIV-1 Treated with Ritonavir-Boosted Fosamprenavir Oral Solution–Based Antiretroviral Therapy

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Abstract

APV20002 was a multicenter, international, open-label study that began in 2003 investigating the pharmacokinetics, efficacy, and safety of ritonavir-boosted fosamprenavir (FPV/r) oral solution (OS) in combination with nucleoside reverse transcriptase inhibitor-based antiretroviral therapy (ART) in participants living with HIV-1 aged 4 weeks to <2 years with a primary endpoint at Week 48 (48W). Participants in APV20002 could continue in the study post-48W until FPV OS was locally available in their countries. Children were required to discontinue after reaching >39 kg or if FPV OS had no clinical benefit. Fifty-nine participants were enrolled; 5/59 received a single FPV OS visit for pharmacokinetic determinations. Most (38/54; 70%) were antiretroviral experienced; 39/59 participants had >48 weeks on treatment, 4/39 of whom discontinued after 48 weeks due to an adverse event (AE). At 48W, 88% of participants had HIV-1 RNA <400 copies/mL by Observed analysis; the proportion with HIV-1 RNA <400 copies/mL remained high (84%–100%) through Week 684. The median CD4⁺ cell count was 1,235 cells/mm³ [$n = 51$] at baseline, 1,690 cells/mm³ ($n = 41$) at Week 48, and 1,280 cells/mm³ ($n = 21$) at Week 180. From baseline to Week 684, 54/59 (92%) participants had ≥ 1 treatment-emergent AE regardless of causality; 42/59 (71%) had a treatment-emergent grade 2–4 AE, predominantly maximum toxicity: grade 2; 21/59 (36%) and 21/59 (36%) had severe or grade 3/4 AEs. From baseline to Week 684, 14/54 (26%) participants met virologic failure (VF) criteria, 9/14 before 48W. HIV from 1/9 VFs through 48W developed treatment-emergent reduced susceptibility to FPV and 1/9 to lamivudine/emtricitabine. Post-48W, 4/5 participants with VF had phenotype results; all were still susceptible to all study drugs at VF. In conclusion, FPV OS-based ART was efficacious and generally well tolerated in this long-running pediatric study through 684 weeks of treatment, with a safety profile consistent with experience in adults and older children.

Keywords: antiretroviral therapy, HIV-1, pediatric, ritonavir–boosted fosamprenavir oral solution

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Introduction

There is an ongoing need for effective and tolerable medicines with well-characterized safety profiles for children living with HIV. According to recent UNAIDS estimates, 39.0 (33.1–45.7) million people globally were living with HIV in 2022, 1.5 (1.2–2.1) million of whom were children aged 0 to 14 years.¹ UNICEF estimated that in 2022, 84,000 (56,000–120,000) children under age 15 died of HIV-related causes globally, and just over half (57% [44%–78%]) of children under the age of 15 living with HIV were receiving antiretroviral therapy (ART).² The number of new HIV infections in children has declined from an estimated 310,000 (210,000–490,000) in 2010 to 130,000 (90,000–210,000) in 2022.¹

In order to provide another protease inhibitor (PI) formulation suitable for young children, the 48-week APV20002 study began enrollment in 2003. Although designed as a 48-week study to evaluate the pharmacokinetics, safety, tolerability, and antiretroviral activity of ritonavir-boosted fosamprenavir (FPV/r; a prodrug of amprenavir) oral solution (OS) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in PI-naïve and PI-experienced pediatric participants living with HIV-1 aged 4 weeks to <2 years, APV20002 continued for over a decade after 48-week primary endpoint analysis cutoff of 5th July 2011. The results from the 48-week primary endpoint data cutoff were previously reported.^{3,4} After the 48-week primary endpoint was achieved, children already enrolled in the study in countries where FPV OS supplies were not locally available had the option to continue until this study closed in March 2022. In this study, we summarize the safety, efficacy, and resistance data collected through the end of study, when the last remaining study participants had been on ART for 684 weeks.

Materials and Methods

Study design

This international, 48-week, phase 2, open-label, two-cohort multicenter study enrolled participants with HIV-1 aged 4 weeks to <2 years across seven sites in South Africa, Mexico, Argentina, and Portugal. The primary objective was to identify FPV/r OS twice-daily (BID) dosage regimens that delivered plasma amprenavir exposures comparable to those effective in adults and to evaluate the safety, tolerability, and antiretroviral response of these regimens over 48 weeks in two cohorts as follows: Cohort 1 (aged 6 months to <2 years at screening) and Cohort 2 (aged 4 weeks to <6 months at screening). Participants could remain in the study beyond Week 48 until FPV OS was approved and commercial supplies were locally available, until the participants no longer derived clinical benefit, or until the participants weighed >39 kg and could utilize commercially available FPV tablets.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board or independent ethics committee for each participating site. Written informed consent was obtained from each child's legal guardian before any study-specific procedures were performed.

Study population

Male and female participants (maximum age at screening: 22 months for Cohort 1 and 4 months for Cohort 2) with a screening plasma HIV-1 RNA of >400 copies/mL were eligible for enrollment and were either (1) PI-naïve (defined as having received less than one week of any PI, excluding amprenavir, regardless of length of therapy with NRTIs and/or non-nucleoside reverse transcriptase inhibitors [NNRTIs], including completely ART-naïve) or (2) PI-experienced (defined as having prior experience with no more than three PIs, excluding amprenavir). Children were excluded from participation in the study if they had previously received amprenavir.

Children were also excluded from participation if they had a serious medical condition that might compromise safety, had received therapy with NNRTIs in the 14 days before study drug administration, had (within 28 days of commencing the study) grade 3 or 4 alanine aminotransferase and/or aspartate aminotransferase levels, or met other previously reported exclusion criteria.

Drugs and doses

As previously reported,³ approximately 10 participants enrolled in each cohort underwent a single-dose visit (SDV) of FPV and FPV/r for PK assessments to select individualized repeat-dosage regimens. A higher single dose of FPV/r 45/7 mg/kg was implemented for PK evaluation in the 4 weeks to <6 months age cohort, whereas the 6 months to <2 years SDV participants received a single dose of FPV 30 mg/kg at the first SDV and a single dose of FPV/r 30/6 mg/kg at the second SDV. The final dose regimens were 45/7 mg/kg in the 6 months to <2 years and 45/10 mg/kg in the 4 weeks to <6 months cohorts. Once a participant was over 2 years of age, FPV/r dosing was adjusted based upon the participant's weight; FPV/r 23/3 mg/kg BID dosing was used until the participant was >6 years, after which FPV/r dosing was transitioned to 18/3 mg/kg BID. The maximum allowed FPV dose was 700 mg BID, and the maximum ritonavir dose was 100 mg BID. Ritonavir was locally sourced and provided by ViiV Healthcare, initially as OS and subsequently as oral powder sachets after the manufacturer discontinued OS; FPV/r was dosed in combination with two NRTIs. ViiV Healthcare provided participants with abacavir and lamivudine (initially as OS and subsequently as tablets) as an optional background NRTI therapy, given as per the label recommendations; any other NRTIs utilized were obtained on prescription.

Study evaluations

Post-screening, participants were evaluated at baseline; Weeks 2, 4, 8, 12, 16, 24, 36, and 48; and every 12 weeks thereafter. Participants who discontinued study medication completed a follow-up visit after 4 weeks. Safety evaluations, including hematology, clinical chemistry (including lipid panel), and adverse events (AEs), were conducted at every visit; samples for lipid evaluations were not collected under fasting conditions due to the young age of the participants. Division of AIDS toxicity tables was used for severity grading.⁵ Antiretroviral response assessments, including quantitative plasma HIV-1 RNA, lymphocyte subsets, and HIV-1-associated conditions, were carried out at each visit.

Where possible, plasma samples were collected for resistance testing. HIV-1 genotypic and phenotypic analyses were attempted at baseline and virologic failure (VF) time points. HIV-1 genotyping and phenotyping were performed by Monogram Biosciences (South San Francisco, CA). Additional PK assessments were not performed after the Week 48 primary endpoint analysis.³

Statistical analysis

As this was a noncomparative study, no formal statistical hypothesis testing was performed. Snapshot and "Observed" analyses were used for the summary of proportion of participants achieving plasma HIV-1 RNA concentration <400 and <50 copies/mL at Week 48.³ An Observed analysis summarized the proportion of participants achieving plasma HIV-1 RNA concentration <400 and <50 copies/mL from baseline through the end of the study. VF was defined as failure to achieve a plasma HIV-1 RNA of <400 copies/mL by Week 24 or confirmed HIV-1 RNA rebound to ≥ 400 copies/mL at any time after achieving a plasma HIV-1 RNA of <400 copies/mL; participants who met VF criteria were not required to be withdrawn from the study. AE terms provided by the sites were tabulated by the AE preferred term.

Results

Fifty-nine participants received at least one dose of FPV (safety population); five participants discontinued after the SDV PK assessment was performed; and the remaining 54 participants composed the intent-to-treat-exposed population. Briefly, 44 participants were from South Africa, 8 from Mexico, and 1 each from Argentina and Portugal. All acquired HIV-1 perinatally. Overall, of the 54 participants who received more than an SDV of FPV OS, 31 (57%) were female, 23 (43%) were male, 44 (81%) were Black, 8 (15%) were American Indian, and 2 (4%) were White/Caucasian (Table 1). The median age was 6 months (range: 2, 24) at baseline, and 38/54 (70%) were ART experienced, including five participants who received PIs together with other antiretrovirals (ARVs) for 3 to 15 months before study entry. Baseline HIV-1 RNA was 5.60 log₁₀ copies/mL (23/54 had HIV-1 RNA >500,000 copies/mL); baseline CD4⁺ cell count was 1,235 cells/mm³.

The planned duration of the study was 48 weeks; participants who completed through Week 48 on treatment were considered to have completed the study, but some participants were eligible to continue the study after Week 48 if FPV OS was not locally available. A total of 15/54 (28%) participants discontinued treatment on or before Week 48 due to AEs ($n = 2$), insufficient viral load response ($n = 2$), lost to follow-up (LTFU; $n = 3$), protocol violation ($n = 1$), withdrawn from study ($n = 1$), and other ($n = 6$; 1/6 was misclassified as "other," but was discontinued due to pulmonary tuberculosis).

An additional 14 (26%) continued treatment after Week 48, but discontinued before primary endpoint cutoff (5 July, 2011) due to AEs ($n = 1$), insufficient viral load response ($n = 1$), LTFU ($n = 1$), withdrew ($n = 1$), and other (including meeting VF criteria; $n = 10$). Twenty-five participants from South Africa continued the study after the primary endpoint cutoff date. Of these, 3/25 participants continued until study

TABLE 1. BASELINE DEMOGRAPHICS OF APV20002 STUDY PARTICIPANTS

Parameter	Total (n = 54)
Age, median (range), months	6 (2, 24)
Sex, n (%)	
Female	31 (57)
Male	23 (43)
Race, n (%)	
Black	44 (81)
White/Caucasian	2 (4)
Other race (American Indian)	8 (15)
Ethnicity, n (%)	
Hispanic or Latino	9 (17)
Non-Hispanic or Latino	45 (83)
Plasma HIV-1 RNA, median (IQR), log ₁₀ copies/mL	5.60 (5.00, 6.15)
HIV-1 RNA copies/mL, n (%)	
<400	1 (2)
400 to <5000	5 (9)
5000 to <100,000	8 (15)
100,000 to <250,000	5 (9)
250,000 to <500,000	12 (22)
$\geq 500,000$	23 (43)
Absolute CD4 ⁺ cell count, median (IQR), cells/mm ³	1,235 (937, 1795)
Percentage of CD4 ⁺ cells, median (IQR)	26 (18, 34)
Percentage of CD4 ⁺ cells, n (%)	
<15	7 (13)
15 to <25	18 (33)
≥ 25	26 (48)
Any prior antiretroviral therapy, n (%)	38 (70)
Number of NRTIs taken, n (%)	
1	28 (52)
2	7 (13)
3	1 (2)
Number of NNRTIs taken, n (%)	
1	31 (57)
Number of PIs taken, n (%)	
1	4 (7)
2	1 (2)
Duration of NRTI exposure, median (IQR), weeks	1 (1, 4)
Any NRTI, n (%)	36 (67)
Abacavir	1 (2)
Didanosine	1 (2)
Lamivudine	8 (15)
Stavudine	2 (4)
Zidovudine	33 (61)
Duration of NNRTI exposure, median (IQR), weeks	0.1 (0.1, 0.1)
Any NNRTI, n (%)	31 (57)
Nevirapine	31 (57)
Duration of PI exposure, median (IQR), weeks	39 (16, 64)
Any PI, n (%)	5 (9)
Lopinavir/Ritonavir	2 (4)
Nelfinavir	3 (46)
Ritonavir	1 (2)

IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

closure and transitioned to locally available ART; of the remaining 22/25 participants, 10/25 left after achieving a weight >39 kg, 5 were withdrawn (including 1 who met VF criteria), 3 discontinued due to AEs, and 4 withdrew for other reasons.

The median time of exposure to FPV/r BID for all participants ($n = 54$) was 789 days (interquartile range [IQR]: 365, 3,844), with 24 (44%) participants receiving therapy for over 144 weeks, including 14/26 (54%) in the 4 weeks to <6 months age group and 10/28 (36%) in the 6 months to <2 years age group. The numbers of participants who remained in the study post-48 weeks gradually decreased over time as FPV OS became locally available and as participants grew and increased in weight.

Antiretroviral efficacy

The study population had a very high median viral load at baseline (5.6 log₁₀ copies/mL; IQR: 5.00, 6.15). After 24 weeks on FPV/r-based treatment, the median plasma HIV-1 RNA level declined to below the lower limit of detection of the assay (1.69 log₁₀ copies/mL) or <50 copies/mL using the Roche Amplicor HIV-1 Monitor™ Test (Roche Diagnostic Systems Inc, Branchburg, NJ). The median HIV-1 RNA levels remained below the lower limit of detection of the assay (1.69 log₁₀ copies/mL) at Week 36 and Week 48.

After Week 48 through Week 684, the median plasma HIV-1 RNA for participants still in the study remained below the lower limit of detection of the Amplicor assay or the subsequent Abbott RealTime HIV-1 assay (Abbott Molecular Inc, Des Plaines, IL; 1.59 log₁₀ copies/mL or <40 copies/mL). By the Observed analysis, 88% of participants had HIV-1 RNA <400 copies/mL at Week 48, with the proportion of participants with HIV-1 RNA <400 copies/mL remaining high (84%–100%) through Week 684 (Fig. 1). Similarly, by Week 48, 79% of participants (33/42) still on the study had plasma HIV-1 RNA levels of <50 copies/mL. From Week 84 to Week 684, ≥88% of participants at each subsequent analysis time point had plasma HIV-1 RNA levels of <50 copies/mL.

The median CD4⁺ cell count at baseline was 1,235 cells/mm³ ($n = 51$) and increased by Week 48 to 1,690 cells/mm³ ($n = 41$). By Week 180, the median CD4⁺ cell count was 1,280 cells/mm³ ($n = 21$). Normal age-related decline in CD4⁺ cell count was observed over the >10-year study span;

median CD4⁺ cell count was 1,112 cells/mm³ ($n = 17$) at Week 360, 1,064 cells/mm³ ($n = 12$) at Week 480, 866 cells/mm³ ($n = 8$) at Week 600, and 580 cells/mm³ ($n = 1$) at Week 684.

At baseline, the median CD4⁺ cell count measured for the 4 weeks to <6 months at study entry group was slightly higher (1,378 cells/mm³ [$n = 23$]) versus the 6 months to <2 years at study entry group (1,120 cells/mm³ [$n = 28$]); however, the CD4⁺ cell count response was similar for both groups. The median CD4⁺ cell count increased by Week 48 for both age groups (1,690 cells/mm³ [$n = 17$] and 1,602 cells/mm³ [$n = 24$], respectively) and remained elevated compared with baseline through Week 180 (1,332 cells/mm³ [$n = 12$] and 978 cells/mm³ [$n = 9$], respectively). For the 4 weeks to <6 months at study entry group, the median CD4⁺ cell count was 1,151 cells/mm³ ($n = 10$) at Week 360, 1,064 cells/mm³ ($n = 6$) at Week 480, 866 cells/mm³ ($n = 6$) at Week 600, and 750 cells/mm³ ($n = 1$) at Week 660. For the 6 months to <2 years at study entry group, the median CD4⁺ cell count was 962 cells/mm³ ($n = 7$) at Week 360, 1,010 cells/mm³ ($n = 6$) at Week 480, 717 cells/mm³ ($n = 2$) at Week 600, and 580 cells/mm³ ($n = 1$) at Week 684.

Safety

Overall, 92% (54/59) of participants reported at least one AE through the end of the study (97% [29/30] in the 6 months to <2 years cohort and 86% [25/29] in the 4 weeks to <6 months cohort). AEs occurring in more than 10% of participants overall are shown in Table 2.

Of the 59 study participants, 42 (71%) had a treatment-emergent grade 2 through grade 4 AE. The AEs reported were predominantly grade 2 (36%, $n = 21$) in severity, followed by grade 3 (25%, $n = 15$), with a smaller number reporting grade 4 events (10%, $n = 6$). The system organ class with the highest incidence of grade 2 through grade 4 AEs was infections and infestations (54%, 32/59). The most frequent events were gastroenteritis (17%, $n = 10$), blood cholesterol increased (14%, $n = 8$), and pneumonia (14%, $n = 8$); all other grade 2 through grade 4 AEs occurred at a frequency of <10% of participants.

Drug-related treatment-emergent AEs were experienced by 42% (25/59) of participants, the most common being blood cholesterol increased (22%, 13/59; “blood cholesterol increased” was used when the original term provided

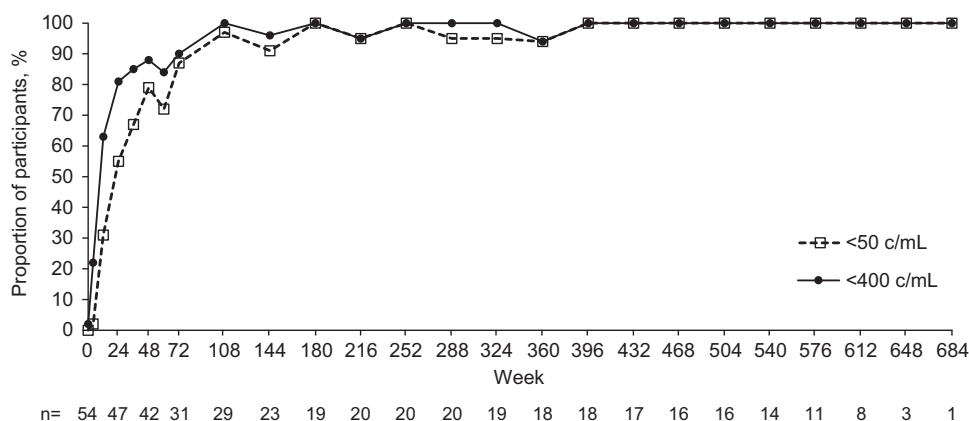


FIG. 1. Proportion of study participants with HIV-1 RNA <50 and <400 copies/mL through Week 684.

TABLE 2. SUMMARY OF ALL TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN >10% OF PARTICIPANTS OVERALL FROM BASELINE TO WEEK 684

n (%)	FPV/r BID (n = 59)
Any event ^a	54 (92)
Diarrhea	34 (58)
Upper respiratory tract infection	27 (46)
Otitis media ^b	26 (44)
Gastroenteritis	24 (41)
Cough	21 (36)
Pharyngitis	21 (36)
Rhinitis	20 (34)
Nasopharyngitis	17 (29)
Vomiting	16 (27)
Tonsillitis	14 (24)
Blood cholesterol increased ^c	13 (22)
Eczema	13 (22)
Dental caries	12 (20)
Conjunctivitis	11 (19)
Impetigo	10 (17)
Pneumonia	9 (15)
Seborrheic dermatitis	9 (15)
Tinea capitis	9 (15)
Acarodermatitis	7 (12)
Dermatitis diaper	7 (12)
Helminthic infection	7 (12)
Oral herpes	7 (12)

^aAdverse event terms provided by the sites were tabulated by the adverse event preferred term.

^bThe terms otitis media and otitis media acute have been combined.

^cLipid evaluation samples were not collected under fasting conditions due to the young age of the participants.

BID, twice daily; FPV/r, ritonavir-boosted fosamprenavir.

by the site contained elevated, increased, high, or a similar modifier), hypercholesterolemia (10%, 6/59), blood cholesterol (8%, 5/59), blood triglyceride increased (7%, 4/59), diarrhea (7%, 4/59), and vomiting (5%, 3/59). Drug-related treatment-emergent AEs were predominantly maximum toxicity of grade 1 (19%, 11/59) and grade 2 (17%, 10/59) in severity, followed by a smaller number for grade 3 (5%, 3/59) and grade 4 (2%, 1/59) events.

Through Week 684, 21 participants (36%) reported severe or grade 3/4 treatment-emergent AEs overall, with infections and infestations (24%, 14/59) the most common system organ class (Table 3). Pneumonia ($n = 6$), gastroenteritis ($n = 5$), neutropenia ($n = 3$), blood creatine phosphokinase increased ($n = 2$), hypertension ($n = 2$), and urinary tract infection ($n = 2$) were events reported by more than one participant (Table 3). Five participants reported grade 3/4 AEs with onset dates after 5th July 2011; none of these was considered related to the study medications. These events were gastroenteritis (nonserious AE, grade 3), tuberculosis (serious AE, grade 3), dehydration (serious AE, grade 3), arthritis bacterial (serious AE, grade 3), and, in one participant, neutrophil count decreased (two grade 3 and two grade 4 nonserious AEs) and neutropenia (serious AE, grade 4).

A total of 42% (25/59) of participants experienced treatment-emergent serious AEs (Table 4). By system organ class, the most frequent of these were in the infections and

TABLE 3. SUMMARY OF TREATMENT-EMERGENT GRADE 3/4 ADVERSE EVENTS BY FREQUENCY FOR ALL STUDY PARTICIPANTS THROUGH WEEK 684

n (%)	FPV/r BID (n = 59)
Any event	21 (36)
Pneumonia	6 (10)
Gastroenteritis	5 (8)
Neutropenia	3 (5)
Blood creatine phosphokinase increased	2 (3)
Hypertension	2 (3)
Urinary tract infection	2 (3)
Alanine aminotransferase increased	1 (2)
Anogenital warts	1 (2)
Arthritis bacterial	1 (2)
Bronchiolitis	1 (2)
Dehydration	1 (2)
Febrile convulsion	1 (2)
Greenstick fracture	1 (2)
Herbal toxicity	1 (2)
Hypernatremia	1 (2)
Hypertransaminasemia	1 (2)
Inflammation	1 (2)
Kwashiorkor	1 (2)
Lower respiratory tract infection	1 (2)
Meningitis	1 (2)
Meningitis bacterial	1 (2)
Neutrophil count decreased	1 (2)
Pneumonia viral	1 (2)
Pneumonitis chemical	1 (2)
Thrombocytopenia	1 (2)
Tracheobronchitis	1 (2)
Tuberculosis	1 (2)
Vomiting	1 (2)

BID, twice daily; FPV/r, ritonavir-boosted fosamprenavir.

infestations class (32%, 19/59). Serious AEs that were reported for more than one participant included pneumonia ($n = 9$), gastroenteritis ($n = 6$), hypertension ($n = 2$), neutropenia ($n = 2$), seizure ($n = 2$), and urinary tract infection ($n = 2$). Six participants reported following serious AEs that had onset dates after 5th July 2011 and that were not considered related to investigational product: iridocyclitis (grade 2), tuberculosis (grade 2), thermal burn (grade 2), neutropenia (grade 4), and arthritis bacterial (grade 3) were each observed in a single participant; in the sixth participant, three serious AEs were observed, including dehydration (grade 3), gastroenteritis (grade 3), and hydrocele (grade 1).

Three participants (6%) experienced HIV disease progression to a new Centers for Disease Control and Prevention Class C or death while on study medications; all occurred before the Week 48 endpoint cutoff of 5th July 2011. One participant progressed from Class A to Class C (HIV-related encephalopathy). Two deaths occurred while participants were on study medication: septicemia in one participant (not considered drug-related) and gastroenteritis in the second participant (considered possibly drug-related) and herbal toxicity (not considered drug-related). An additional participant died after an acute abdominal disorder occurring 11 days after having received the SDV of FPV and FPV/r; this death was not considered drug-related.

TABLE 4. SUMMARY OF TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS FOR ALL STUDY PARTICIPANTS FROM BASELINE TO WEEK 684

n (%)	FPV/r BID (n = 59)
Any event ^a	25 (42)
Pneumonia	9 (15)
Gastroenteritis	6 (10)
Hypertension	2 (3)
Neutropenia	2 (3)
Seizure	2 (3)
Urinary tract infection	2 (3)
Abdominal symptom	1 (2)
Anogenital warts	1 (2)
Arthritis bacterial	1 (2)
Bronchiolitis	1 (2)
Dehydration	1 (2)
Diarrhea	1 (2)
Escherichia urinary tract infection	1 (2)
Febrile convulsion	1 (2)
Greenstick fracture	1 (2)
Herbal toxicity	1 (2)
Hydrocele	1 (2)
Hypernatremia	1 (2)
Hypertransaminasemia	1 (2)
Inflammation	1 (2)
Iridocyclitis	1 (2)
Kwashiorkor	1 (2)
Lower respiratory tract infection	1 (2)
Malnutrition	1 (2)
Mastoiditis	1 (2)
Meningitis	1 (2)
Meningitis bacterial	1 (2)
Otitis media chronic	1 (2)
Pneumonia viral	1 (2)
Pneumonitis chemical	1 (2)
Thermal burn	1 (2)
Tracheobronchitis	1 (2)
Tuberculosis	1 (2)

^aSerious adverse events that were considered by the site physicians to be drug related were as follows: gastroenteritis ($n = 1$, 2%), febrile convulsion ($n = 1$, 2%), and hypertransaminasemia (transaminases increased; $n = 1$, 2%).

BID, twice daily; FPV/r, ritonavir-boosted fosamprenavir.

Ten of 51 (20%) participants had a grade 3 treatment-emergent clinical chemistry maximum toxicity result. Two of 51 (4%) participants had a grade 4 treatment-emergent clinical chemistry maximum toxicity result through the end of the study. Five of 51 (10%) participants had a grade 3 treatment-emergent hematology maximum toxicity result, and 2/51 (4%) had a grade 4 treatment-emergent hematology maximum toxicity result through the end of the study. Most of these occurred before the cutoff of 5 July, 2011.³ Two participants had treatment-emergent grade 3 or 4 clinical chemistry abnormalities relating to blood samples taken after 5 July, 2011; one participant had grade 3 hypernatremia at Week 492 (with no elevated sodium values at other time points), and a second participant had grade 4 hyperkalemia at Week 264 (who had subsequent values in the normal range, a grade 3 hyperkalemia at Day 1 pretreatment, and a number of potassium values above the normal range during this study). Two participants had treatment-emergent grade 3

or 4 hematology abnormalities relating to blood samples taken after 5 July, 2011, including one with grade 3 low white blood cell value (at Week 660), five grade 3 low total neutrophil values (at Weeks 168, 480, 516, 672, and 684), and three grade 4 low total neutrophil values (two at Week 660 and one at Week 684). The timings of relevant AEs (serious AE of neutropenia or nonserious AEs of neutrophil count decreased) not considered related to study treatment overlapped with the timing of the grade 4 and two of the grade 3 low total neutrophil values. Although there were some low values subsequently, the white blood cell count improved at later time points, and total neutrophil values improved at visits during the follow-up phase. The second participant had four grade 3 low total neutrophil count (Weeks 300, 360, 420, and 456), but these values improved at subsequent visits.

No participants developed abacavir-related hypersensitivity. One participant was confirmed positive for COVID-19 but was asymptomatic.

Virology

Fourteen of 54 (26%) participants met VF criteria from baseline through Week 684; nine of these (17%) by Week 48. The HIV-1 genotypic and phenotypic analysis results for these nine VFs were previously described.^{3,4} At baseline, 6/9 participants who subsequently met VF criteria had HIV-1 RNA $\geq 250,000$ copies/mL; 7/9 were ART-experienced prior to study enrollment and 6/9 met VF criteria by failing to suppress to <400 copies/mL by Week 24.⁴ Of these, 7/9 had paired HIV-1 genotypes and phenotypes available at baseline and VF. Briefly, HIV-1 from 1/7 participants with paired results selected the M184V mutation at VF with concomitant reduced susceptibility to lamivudine, with 3/7 participants having treatment-emergent minor HIV-1 protease mutations at VF (with respect to drug resistance to FPV/r). One of seven participants, who was ART-experienced with prior PI exposure at baseline, had reduced susceptibility to FPV and ritonavir at VF.

For the five participants who met VF criteria after Week 48, three participants had paired baseline and VF genotypic and phenotypic results. The fourth participant had a VF genotype and phenotype but no baseline sample, whereas the fifth participant met VF criteria but had only baseline results. At baseline, 2/5 of these participants who subsequently met VF criteria had HIV-1 RNA $\geq 250,000$ copies/mL and 4/5 were ART-experienced prior to study enrollment.

The first participant was 7 months of age at study entry, ART-experienced but PI-naïve. At baseline, the HIV-1 protease mutations M361, L89M, and I93L, but no reverse transcriptase (RT) mutations, were detected; these mutations were maintained at VF (Week 60), and no additional treatment-emergent mutations were detected. Both the baseline and VF samples were phenotypically susceptible to all ARVs. The second participant was 15 months of age at study entry and ART-naïve. No resistance-associated RT mutations and the K20R, M361, L63P, V77I, L89M, and I93L protease mutations were detected at baseline. Two additional treatment-emergent minor PI mutation mixtures, L10L/R and I62I/V, were detected at Week 156. Both the baseline and VF samples were phenotypically susceptible to all ARVs. The third participant was 3 months of age at study

entry and ART-experienced but PI-naïve. Only protease mutations (M36I, L89M, and I93L) were detected at baseline. No additional treatment-emergent mutations were detected at VF (Week 84). Both the baseline and VF samples were phenotypically susceptible to all ARVs. The fourth participant was 2 months of age at study entry and ART-experienced but PI-naïve. No baseline HIV-1 genotypic or phenotypic result was obtained. The participant met VF criteria at Week 72. HIV-1 genotyping detected the NNRTI resistance-associated mutation K103N and the protease mutations M36I, L63P, V82V/A, L89M, and I93L. Reduced susceptibility to nevirapine was detected at VF, but the virus was susceptible to FPV and all other PIs, NNRTIs, and NRTIs. The fifth participant was 4 months of age at study entry and ART-experienced but PI-naïve. Only baseline HIV-1 genotype and phenotype results were obtained; the minor protease mutations M36I, L89M, and I93L were detected, and the viral isolate was phenotypically susceptible to all ARVs.

Discussion

Although APV20002 was atypical in that it continued for more than a decade, enabling these pediatric participants living with HIV-1 to remain on treatment with FPV/r, there was also a 48-week study (APV29005) that evaluated the PK, safety, and antiviral activity of twice-daily FPV or FPV/r that had enrolled a slightly older (2- to 18-year-old) population of children living with HIV-1 who were PI-naïve and ART-experienced.⁶ While this study did not have the duration observed for APV20002 (the median exposure to FPV was 127 weeks [range: 2, 258 weeks], with 88% of participants exposed for >48 weeks), it provides a point of comparison. In APV29005, FPV or FPV/r was administered with a background regimen of two or three active NRTIs with enfuvirtide also permitted in addition to NRTIs for children >6 years old. The proportion of participants with HIV-1 RNA <400 copies/mL at Week 48 was 60% for FPV and 53%–74% for FPV/r (intent-to-treat [exposed], snapshot analysis). Overall, 25 participants (23%) met VF criteria. Of these, 21% (19/89) of participants were receiving FPV/r, and 30% (6/20) were receiving FPV without a boosting agent. Median increases in absolute and relative (percentage) CD4⁺ cell counts from baseline to Week 48 occurred in both the FPV (340 cells/mm³; 8%) and FPV/r group (190 cells/mm³; 8%). The most common AEs were vomiting, cough, and diarrhea; 18 participants experienced serious AEs, including 9 with suspected abacavir hypersensitivity.

By comparison, in the previously published analysis for APV20002, the median time of exposure to FPV/r BID was 77 weeks (range: 2, >144 weeks), with 42 (78%) participants receiving study medication for >48 weeks and 27 (50%) participants for >96 weeks.³ In that analysis, 35 of 54 (65%) FPV/r-treated participants who received more than one dose achieved plasma HIV-1 RNA <400 copies/mL and 33 of 54 (61%) had plasma HIV-1 RNA values <50 copies/mL. Nine participants (17%) met confirmed VF criteria by Week 48. Median CD4⁺ cell percentages in each age cohort improved, with a median change from baseline of +5%. The most common AEs were diarrhea, upper respiratory tract infection, gastroenteritis, and otitis media. Of the 59 participants who were enrolled and received at least one dose of FPV, 19

(32%) reported severe or grade 3/4 treatment-emergent AEs, none of which was suspected abacavir hypersensitivity.

The results from these earlier APV20002 and APV29005 analyses for children who received FPV/r were similar. The results from the current analysis that encompassed up to 684 weeks of treatment for the APV20002 study showed that FPV/r OS was generally well tolerated in this population, with a safety profile consistent with what has been reported in adults and older children. No new safety concerns were identified after the 48-week primary endpoint analysis. The participants who remained in the study after Week 48, with few exceptions, tended to remain virologically suppressed until study exit, which was usually because their weight had increased to >39 kg and they could access the correct dosage of locally available FPV tablets. Few (*n* = 5) participants met VF criteria after 48 weeks of treatment, and none with phenotype results at VF had virus with reduced susceptibility to FPV/r.

FPV/r is unlikely to be chosen as a first-line treatment, as over the years many simpler regimens have become available. However, with its favorable resistance profile, safety, and efficacy, even among ART-exposed participants with VF at study enrollment, FPV/r provides an alternative option in those failing treatment.

Conclusions

Children and adolescents living with HIV face multilevel barriers to retention in care and adherence to ART. These include HIV stigma, socioeconomic factors, family-level challenges, and unmet mental health needs.^{7–10} Although the APV20002 study was designed to evaluate the PK, safety, tolerability, and antiretroviral activity of FPV OS when administered to PI-naïve and PI-experienced pediatric participants living with HIV-1 aged 4 weeks to <2 years through Week 48, this study continued for over a decade after 48-week primary endpoint analysis cutoff. Many of the children in the subset still in the study after 48 weeks were between 10 and 14 years old at study exit. These results serve to highlight the impact that a supportive site staff and caregivers can have in reducing barriers to retention in care and in promoting drug regimen adherence in children and adolescents living with HIV-1.

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Authors' Contributions

L.L.R. and H.P.G. contributed to conceptualization. L.L.R., K.M., and S.K. contributed to formal analysis. L.L.R., M.F.C., H.C., and H.P.G. contributed to investigation. L.L.R. and S.C.v.D. contributed to methodology. J.R. contributed to project administration. L.L.R. contributed to supervision. L.L.R., S.K., S.D., and J.R. contributed to validation. L.L.R. and S.D. contributed to visualization. L.L.R. contributed to writing the original draft. All authors

contributed to reviewing and editing the drafts and approved the article for publication.

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Data Availability Statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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