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Pharmacokinetics and 48-week Safety and Antiviral Activity of Fosamprenavir-containing Regimens in HIV-infected 2- to 18-year-old Children

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Background: Pharmacokinetics, safety and antiviral activity of twice-daily fosamprenavir with or without ritonavir were evaluated in 2- to 18-year-old protease inhibitor–naïve and -experienced HIV-1–infected children.

Methods: Serial pharmacokinetic samples were collected at week 2 and predose samples every 4–12 weeks. Safety and plasma HIV-1 RNA were monitored every 4–12 weeks.

Results: Twenty protease inhibitor–naïve 2- to <6-year-old subjects received antiretroviral treatment including unboosted fosamprenavir twice-daily, whereas 89 protease inhibitor–naïve and -experienced 2- to 18-year-old subjects received fosamprenavir/ritonavir-containing therapy twice-daily. Median fosamprenavir exposure was 891 days (range 15–1805 days), with 88% exposed >48 weeks. Twice-daily doses of fosamprenavir/ritonavir 23/3 mg/kg in 2- to <6-year olds, 18/3 mg/kg in ≥6-year olds and 700/100 mg in adolescents achieved plasma amprenavir exposures comparable with or higher than 700/100 mg twice-daily in adults while fosamprenavir 30 mg/kg twice-daily in 2- to <6-year olds led to exposures higher than 1400 mg twice-daily in adults. The proportion of subjects with HIV-1 RNA <400 copies/mL at week 48 was 60% for fosamprenavir and 53–74% for fosamprenavir/ritonavir (intent-to-treat [exposed], snapshot analysis). Median increases in absolute and relative (percentage) CD4 counts from baseline to week 48 occurred in both the fosamprenavir (340 cells/mm^3; 8%) and fosamprenavir/ritonavir group (190 cells/mm^3; 8%). The most common adverse events were vomiting, cough, and diarrhea; 18 subjects experienced serious adverse events, including 9 with suspected abacavir hypersensitivity.

Conclusions: Fosamprenavir regimens administered to HIV-1–infected children aged 2–18 years were generally well-tolerated and provided sustained antiviral activity over 48 weeks, with plasma amprenavir exposures comparable with or higher than adults.

Key Words: fosamprenavir, HIV-1, children

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Early and effective antiretroviral therapy (ART) has been shown to improve clinical outcomes in children with HIV and reduce early infant mortality.[1–3] Current US and European pediatric treatment guidelines recommend therapy with a combination of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor or protease inhibitor (PI).[4,5] Although several PI therapies are available for treating HIV infection in children, there remains a need for further potent PI therapies in formulations suitable for use in children to be given with an NRTI background.

Fosamprenavir (FPV), the phosphate ester prodrug of the PI amprenavir (APV), was developed to improve the delivery of APV. The safety and efficacy of FPV-containing regimens has been established in adults in 3 phase III clinical studies, including FPV 1400 mg twice-daily (BID) and FPV 1400 mg once-daily (QD) + ritonavir (RTV) 200 mg QD in antiretroviral-naïve adult subjects and FPV 700 mg BID + RTV 100 mg BID in PI-experienced adult subjects.[6–8]

This study, APV29005, evaluates the pharmacokinetics (PK), safety and antiviral activity of oral FPV/RTV BID regimens in combination with NRTIs, in PI-naïve and PI-experienced children 2 to 18 years of age. In addition, unboosted FPV was evaluated in 2- to <6-year-old subjects; unboosted FPV was not studied in older children because doses were established in 6- to <18-year olds based on data from pediatric APV studies.[9–11] Study APV20003 evaluated once-daily dosing of FPV/RTV, but data did not support this dosage regimen in the pediatric patient population leading to the initiation of APV29005.[12,13]

Recruitment into APV29005 commenced in August 2004 and completed during 2010. Subjects have been allowed to continue receiving FPV beyond week 48 until it is approved locally for use in the relevant age group and commercial supplies are available or until the subjects no longer derive clinical benefit. The study is ongoing, and this report presents data up to and including the last subject reaching the week 48 visit.

METHODS

Study Design

This international, 48-week, phase II, open-label, multicohort, multicenter study enrolled HIV-1–infected children, 2 to 18 years of age, across 30 sites in North America, Europe and South Africa. Enrollment of PI-naïve subjects to cohort 1A (FPV, 2 to <6 years) and both PI-naïve and PI-experienced subjects to cohorts 1B, 2 and 3 (FPV/RTV, 2 to <6 years, 6 to <12 years and 12 to 18 years, respectively)

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occurred in parallel. The first 6–10 subjects in each cohort initiated a regimen based on previous APV and FPV pediatric studies; subsequently enrolled subjects received a regimen based on preliminary PK results for these first 6–10 subjects in each cohort (see Drugs and Dosages). A fourth cohort was open to subjects of any age once enrollment into the appropriate age-defined cohort was complete.

The study was approved by the Institutional Review Board or Independent Ethics Committee for each participating site.

Drugs and Doses

Doses tested are summarized (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B636). The initial dose selected for 2- to <6-year-old subjects in cohort 1A was FPV 40 mg/kg BID, twice the initial boosted dose administered in the same age cohort, and consistent with the 2:1 unboosted:boosted ratio in adults. Following exposures that were higher than adults receiving the standard FPV 1400 mg BID regimen, the dose was revised to FPV 30 mg/kg BID (see Results). FPV/RTV 20/4 mg/kg BID was selected as the initial dose for 2- to <6-year-old subjects in cohort 1B to account for ~28% lower APV exposure in APV20003, which compared data for 2- to <6-year-old children receiving FPV/RTV 30/6 mg/kg QD to adults receiving FPV/RTV 1400/200 mg QD. This initial dose was subsequently increased to FPV/RTV 23/3 mg/kg BID based on results of a population PK analysis.[14] An initial dose of FPV/RTV 15/3 mg/kg was selected for 6 to 18 years old subjects in cohorts 2 and 3 based on data from APV20003, which demonstrated comparable APV exposures in 6- to 18-year-old children receiving FPV 30/6 mg/kg QD and in adults receiving FPV/RTV 1400/200 mg QD. Following exposures that were lower than adults receiving the standard FPV/RTV 700/100 mg BID regimen, the dose was revised to FPV/RTV 18/3 mg/kg BID (up to the adult tablet dose of FPV/RTV 700/100 mg BID; see Results).

Subjects were given FPV±RTV with a background regimen of 2 or 3 active NRTIs. Enfuvirtide was permitted in addition to NRTIs for children >6 years old, providing its use was within the locally approved product label. FPV was administered as either 50 mg/mL oral suspension or 700 mg tablets (permitted for children ≥39 kg). RTV was given either as an 80 mg/mL oral solution or as 100 mg capsules (permitted for children ≥33 kg).

Study Population

Written informed consent was obtained from the parent/legal guardian of all children recruited to the study along with the child's verbal assent, wherever possible. Male and female children, 2 to 18 years of age, with a screening plasma HIV-1 RNA of ≥400 copies/mL were recruited.

Subjects were either PI-naïve (defined as having received <1 week of any PI), including both ART-experienced and ART-naïve subjects, or PI-experienced (defined as having received >1 week prior PI therapy with no more than 3 PIs). Prior RTV-boosted PI therapy was considered as 1 PI if the RTV dose was lower than that recommended for use of RTV as an antiretroviral.

Only PI-naïve subjects 2–5 years of age were enrolled into cohort 1A. Subjects were excluded from participation if they had a serious medical condition that might compromise safety, received prior therapy with FPV or APV for >7 days, or had, within 28 days of commencing the study, grade 3 or 4 alanine aminotransferase and/or aspartate aminotransferase levels, or received radiation, cytotoxic chemotherapy, immunomodulatory agents, investigational drugs or concomitant medications where drug interaction could result in unsafe concentrations of the concurrent medication or markedly reduced plasma APV exposure.

Study Evaluations

Subjects were evaluated at screening and/or baseline visits and at weeks 2, 4, 8, 12, 16, 24, 36 and 48, and every 12 weeks thereafter. After discontinuation of study medication, a follow-up assessment was performed 4 weeks after withdrawal. Intensive PK sampling (at 0 hours and at 1, 2, 4, 6, 8 and 12 hours postdose) was performed at week 2; predose samples were collected every 4–12 weeks. Evaluations of safety, including measurement of growth parameters and collection of hematology, clinical chemistry (including lipid panel) and adverse events (AEs) were conducted every 4–12 weeks, together with antiviral activity (plasma HIV-1 RNA and lymphocyte subsets). All study medication was stopped in subjects with a grade 3 or 4 AE or toxicity unless there was compelling evidence that it was not causally related to study medication. ART could have been restarted at full dose in subjects with a drug-related grade 3 AE or toxicity once it returned to ≤grade 2. The Division of AIDS Toxicity Table (2004) was used for severity grading.[15] Where available, samples obtained at initial virologic failure (VF; see Virology Analysis), or the closest sample collected within 12 weeks after VF, and corresponding baseline samples were used for viral genotyping and phenotyping (Monogram BioSciences, South San Francisco, CA).

Statistical Analysis

As this was a noncomparative study, no formal statistical hypothesis testing was performed. The primary study endpoints were plasma APV area under the concentration–time curve over a dosing interval (AUC[0–τ]), maximum concentration (Cmax), and concentration at the end of a dosing interval (Cτ), the proportion of subjects who permanently discontinued FPV/RTV or FPV due to AEs, and the incidence and nature of AEs and laboratory abnormalities. Antiviral response was a secondary endpoint.

Both intent-to-treat (ITT) (exposed) and safety populations included all subjects with documented evidence of having received at least 1 dose of investigational treatment.

Pharmacokinetic Analysis

PK calculations were based on actual dose and recorded sample collection times. PK parameters were calculated for each subject using noncompartmental methods (WinNonlin version 5.2; Pharsight Corporation, Mountain View, CA). Plasma APV and RTV PK parameters included AUC(0–τ), Cmax, Cτ and apparent oral clearance (CL/F). APV and RTV Cτ summaries and comparisons included predose concentrations collected at all visits; AUC(0–τ), Cmax and CL/F summaries and comparisons were based on serial concentration data collected at week 2.

Plasma APV and RTV PK parameters were summarized by age group and dose group; to be included in a dose group, the actual dose must have been within 10% of nominal dose. PK data in children were compared with historical adult datasets comprised of 190 healthy adults receiving FPV 1400 mg BID and 159 healthy adults receiving FPV/RTV 700/100 mg BID. PK parameters were log transformed before analysis by mixed-effect analysis of variance, fitting the combination of age cohort and dosage regimen as a fixed effect. The ratio of geometric least squares means and associated 90% confidence interval was determined for each comparison.

Safety Analysis

AEs, drug-related AEs, serious AEs (SAEs), AEs leading to discontinuation and grade 3/4 laboratory values were summarized by age group and overall.

Antiviral Response Analysis

Snapshot analyses were used for the summary of the proportion of subjects achieving plasma HIV-1 RNA concentrations <400 copies/mL at each visit. Responder or nonresponder classification was determined by the last available HIV-1 RNA assessment within the window of the visit of interest. A subject with missing on-treatment HIV-1 RNA data in the window of the visit of interest was considered a nonresponder as was a subject who switched or added background ART unless there was documented evidence of toxicity and the change was made before the first on-treatment visit where HIV-1 RNA was assessed (week 2).

Virology Analysis

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. Treatment-emergent resistance-associated viral mutations were as defined by the 2010 IAS-USA resistance mutations guidelines.[16]

RESULTS

A total of 110 subjects enrolled in the study; 109 subjects received study medication and were included in the safety and ITT(exposed) populations. Twenty PI-naïve, 2- to <6-year-old subjects received unboosted FPV BID; all others (N = 89) received FPV/RTV BID.

Study Population

Subject age ranged from 2 to 18 years; 55% of subjects were White and 39% Black, and 53% were female. Demographic characteristics were similar across the age groups with respect to ethnicity and gender (Table 1). Higher baseline viral loads were seen in the 2- to 6-year-old subjects receiving unboosted FPV, and CD4+ cell counts were lowest in the 6- to <12-year-old age group, which also included the highest proportion of PI-experienced subjects (Table 1).

Most of the PI-experienced subjects (n = 40) had only 1 prior PI exposure (25/40, 63%), with nelfinavir the most commonly prescribed PI (83%). The median duration of prior PI exposure was 225 weeks.

Exposure to FPV

The median exposure to FPV was 891 days (range 15–1805 days), with 88% subjects exposed >48 weeks. Overall, 23 (21%) subjects discontinued treatment up to and including the week 48 assessment window, including 2 subjects receiving unboosted FPV, and 24 (22%) discontinued after week 48. The reasons for the discontinuations through week 48 were AEs (n = 3), consent withdrawn (n = 2), insufficient viral load response (n = 1) and "other" (n = 17), including 8 from 1 site where the investigator had decided to withdraw subjects at the week 48 visit, adherence/compliance issues (n = 6), switch to commercially available FPV (n = 1), subject management criteria met (n = 1) and prohibited medication required (n = 1). Of the 24 discontinuations after week 48, 9 (38%) were due to insufficient viral load response (including 4 subjects in the FPV group) and none due to AEs.

Pharmacokinetics

APV exposures in subjects 2 to <6 years of age receiving FPV 40 mg/kg BID were higher than adult s receiving the standard FPV 1400 mg BID regimen (Table 2). Due to the relatively high APV Cτ and the desire to reduce dose volumes, the dose was decreased to FPV 30 mg/kg BID. FPV 30 mg/kg BID delivered 27% higher plasma APV AUC(0–τ), 41% higher Cmax and 90% higher Cτ values in 2- to <6-year-old subjects than historically observed in adults receiving FPV 1400 mg BID (Table 2).

Compared with the historical adult population receiving FPV/RTV 700/100 mg BID, the 2- to <6-year olds who received FPV/RTV 23/3 mg/kg BID achieved approximately 50% higher plasma APV AUC(0–τ), Cmax and Cτ values (Table 2). APV AUC(0–τ) and Cmax following FPV/RTV 15/3 mg/kg BID in 6- to <12-year olds in cohort 2 and 12- to 18-year olds in cohort 3 were lower than adults receiving the standard FPV/RTV 700/100 mg BID regimen (Table 2), and the dose was increased to FPV/RTV 18/3 mg/kg BID. The 6- to <12-year olds receiving FPV/RTV 18/3 mg/kg BID had 12% to 31% higher AUC(0–τ), Cmax and Cτ values compared with adults (Table 2). The majority (13/17) of 12- to 18-year-old subjects met the minimum weight criteria of 39 kg and received the standard adult FPV/RTV 700/100 mg BID regimen and achieved plasma APV exposures similar to the historical adult population (Table 2). APV PK parameters for all age groups administered FPV/RTV doses are displayed (see Fig., Supplemental Digital Content 2, http://links.lww.com/INF/B637).

RTV 3 mg/kg BID, in combination with FPV, delivered higher plasma RTV Cτ across the age groups (see Table, Supplemental Digital Content 3, http://links.lww.com/INF/B638).

FPV was rapidly and extensively converted to APV, and plasma FPV prodrug concentrations were undetectable in the majority (98%) of samples; quantifiable FPV prodrug concentrations were low, ranging from 0.005 μg/mL to 0.129 μg/mL.

Safety

Small increases in median height and weight Z scores were seen at week 48 for both the FPV and FPV/RTV treatment groups. Overall, AEs were reported by 95% (19/20) and 93% (83/89) of subjects in the FPV and FPV/RTV treatment groups, respectively; the frequency of AEs was broadly similar across the age groups (Table 3).

Thirty-nine percent (42/109) of subjects reported at least 1 drug-related AE with vomiting (21%, 23/109), diarrhea (8%, 9/109) and nausea (6%, 7/109) most commonly reported. In the FPV/RTV group, there were no appreciable differences in drug-related AEs in the 12- to 18-year olds and 6- to <12-year olds (38%, 15/40, and 43%, 13/30, respectively). The majority of drug-related diarrhea and nausea were reported in the adolescent group (18%, 7/40 and 15%, 6/40, respectively). The proportion of 2- to <6-year olds reported to have experienced at least 1 drug-related AE was 11% (2/19) in the FPV/RTV group but 60% (12/20) in the FPV group; the higher incidence of drug-related AEs in the FPV group was primarily due to reports of vomiting.

Eleven percent (12/109) of subjects experienced at least 1 drug-related grade 2–4 AE, 11% (10/89) of subjects in the FPV/RTV group and 10% (2/20) of subjects in the FPV group. Gastrointestinal disorders were the most common drug-related grade 2–4 AEs (6%, 6/109) with all episodes reported for subjects in the FPV/RTV group. Three percent (3/89) of subjects experienced grade 2–4 vomiting and 2% (2/89) grade 2–4 diarrhea (1 of whom also reported drug-related grade 2 nausea). The incidence of drug-related vomiting was highest in the 2- to <6-year olds in the FPV group (50%, 10/20; all grade 1) and 6- to <12-year olds in the FPV/RTV group (30%, 9/30; 7 grade 1 and 2 grade 2) compared with the 2- to <6-year olds and 12- to 18-year olds in the FPV/RTV group (5%, 1/19, grade 2; 8%, 3/40, all grade 1). Eighteen subjects (17%) experienced at least 1 SAE; the SAEs reported by more than 1 subject were abacavir drug hypersensitivity (8%, 9/109), pneumonia (3%, 3/109) and respiratory tract infection (2%, 2/109). Two SAEs, reported at different time points in the same subject, were judged by the investigator to be related to FPV/RTV: drug

TABLE 1. Demographic and Baseline Characteristics

	FPV	FPV/RTV			Total
	2 to <6 yr (N = 20)	2 to <6 yr (N = 19)	6 to <12 yr (N = 30)	12 to 18 yr (N = 40)	2 to 18 yr (N = 109)
Age in yr, median (min, max)	2.5 (2, 5)	4.0 (2, 5)	8.5 (5, 11)	14 (12, 18)	9 (2, 18)
Sex, n (%)					
Female	15 (75)	7 (37)	16 (53)	20 (50)	58 (53)
Male	5 (25)	12 (63)	14 (47)	20 (50)	51 (47)
Ethnicity, n (%)					
Hispanic or Latino	0	2 (11)	6 (20)	7 (18)	15 (14)
Not Hispanic or Latino	20 (100)	17 (89)	24 (80)	33 (83)	94 (86)
Weight in kg, range (median Z score)	11–19 (0.22)	10–30 (0.11)	14–62 (0.56)	24–104 (0.10)	—
Height in cm, range (median Z score)	78–106 (−0.21)	79–115 (−0.40)	102–151 (0.20)	126–175 (−0.75)	—
Race, n (%)					
Arabic/North African	0	1 (5)	0	0	1 (<1)
Black	0	14 (74)	9 (30)	20 (50)	43 (39)
South Asian	0	0	0	1 (3)	1 (<1)
White/Caucasian	19 (95)	4 (21)	19 (63)	18 (45)	60 (55)
Other	1 (5)	0	2 (7)	1 (3)	4 (4)
Baseline HIV-1 RNA	n = 20	n = 19	n = 29	n = 40	n = 108
Median plasma HIV-1 RNA $\log_{10}$ copies/mL (IQR)	5.1 (4.9, 5.6)	4.7 (4.4, 5.3)	4.6 (4.1, 5.1)	4.7 (4.1, 5.2)	4.8 (4.2, 5.2)
HIV-1 RNA copies/mL, n (%)					
400–<5000	1 (5)	1 (5)	5 (17)	4 (10)	11 (10)
5000–<100,000	6 (30)	11 (58)	15 (52)	23 (58)	55 (51)
100,000–<250,000	7 (35)	4 (21)	7 (24)	8 (20)	26 (24)
250,000–<500,000	2 (10)	1 (5)	2 (7)	2 (5)	7 (6)
≥500,000	4 (20)	2 (11)	0	3 (8)	9 (8)
Baseline CD4+ cell counts (absolute)	n = 19	n = 19	n = 30	n = 40	n = 108
Median CD4+ cells/mm^3 (IQR)	810 (460, 1000)	915 (608, 1160)	470 (290, 720)	250 (100, 397)	460 (255, 785)
Median % CD4+ cells (IQR)	19 (18, 27)	26 (21, 30)	25 (15, 30)	15 (9, 29)	21 (13, 29)
% CD4+ cells, n (%)					
<15	2 (11)	1 (5)	7 (23)	20 (50)	30 (28)
15–<25	11 (58)	7 (37)	8 (27)	9 (23)	35 (32)
25–<50	6 (32)	11 (58)	13 (43)	11 (28)	41 (38)
≥50	0	0	2 (7)	0	2 (2)
Centers for Disease Control and Prevention classification in children <13 years of age, n (%)	n = 20	n = 18	n = 30	n = 8	n = 76
A: Mildly symptomatic	18 (90)	10 (56)	14 (47)	2 (25)	44 (58)
B: Moderately symptomatic	1 (5)	7 (39)	6 (20)	2 (25)	16 (21)
C: Severely symptomatic	0	1 (6)	7 (23)	2 (25)	10 (13)
N: Nonsymptomatic	1 (5)	0	3 (10)	2 (25)	6 (8)
Centers for Disease Control and Prevention classification in adults/adolescents, n (%)	N/A	N/A	N/A	n = 31	n = 31
A: Asymptomatic or lymphadenopathy or acute HIV	—	—	—	12 (39)	12 (39)
B: Symptomatic, not AIDS	—	—	—	14 (45)	14 (45)
C: AIDS	—	—	—	5 (16)	5 (16)
ART/PI status, n (%)					
ART-naïve	18 (90)	7 (37)	2 (7)	14 (35)	41 (38)
ART-experienced/PI-naïve	2 (10)	6 (32)	8 (27)	12 (30)	28 (26)
PI-experienced	0	6 (32)	20 (67)	14 (35)	40 (37)

IQR indicates interquartile range.

hypersensitivity, considered by the investigator to be an abacavir hypersensitivity reaction, and adverse drug reaction (rash, fever, headache, swollen lips), which occurred after abacavir had been discontinued and was considered likely due to co-trimoxazole. There were no fatal events.

Four subjects from the FPV/RTV group and none from the FPV group experienced an AE leading to permanent discontinuation of study drug and withdrawal from the study. One of these AEs was reported in 2- to <6-year olds (vomiting), 1 in 6- to <12-year olds (hypertriglyceridemia) and 2 in 12- to 18-year olds (adverse drug reaction and pyelonephritis). The reason for discontinuing study drug in the subject with pyelonephritis was also recorded as insufficient viral load response.

The overall incidence of treatment-emergent grade 3/4 laboratory abnormalities was 21% (22/107) (see Table, Supplemental Digital Content 4, http://links.lww.com/INF/B639). Grade 3/4 levels of alanine aminotransferase and/or aspartate aminotransferase were reported in 6 subjects (6/107, 6%) and were not associated with raised bilirubin levels. In 4 subjects the onset occurred at week 72 or beyond, and in 2 subjects at week 12. The abnormal transaminases returned to normal in 3 subjects while they were still receiving study drug. Of the remaining 3 subjects, 2 had underlying hepatitis C. Grade 3/4 neutropenia was reported in 15 of 104 subjects (14%). Most cases developed late in the study, with a median onset of 444 days (range 22 to 1515 days); 10 subjects experienced grade 3/4 neutropenia at week 48 or beyond, 7 of whom at week 108 or beyond. Most of the subjects (n = 14) had 1 event of neutropenia or 2 events with normal values in between. In the FPV/RTV group, there were no reports of grade 3/4 hypertriglyceridemia; grade 3 increases in total cholesterol were reported in 2 subjects (5%) and grade 3 increases in low density lipoprotein cholesterol in 4 subjects (9%). There were no grade 3/4 reports of hypertriglyceridemia,

TABLE 2. Summary of Steady State Plasma APV Pharmacokinetic Parameters in Pediatric Subjects 2 to 18 Years of Age and Statistical Comparison to Historical Adults

Plasma APV PK Parameter	FPV			FPV/RTV			
	Historical Adult 1400 mg BID N = 189	2 to <6 yr		Historical Adult 700/100 mg BID N = 159	2 to <6 yr	6 to <12 yr		12 to 18 yr
		30 mg/kg BID N = 9	40 mg/kg BID N = 7		23/3 mg/kg BID N = 14	15/3 mg/kg BID N = 10	18/3 mg/kg BID N = 12	700/100 mg BID N = 13
AUC(0–τ)* (h·μg/mL)	17.6 (16.7–18.5)	22.3 (15.3–32.6)	24.1 (15.2–38.0)	37.0 (35.1–38.9)	55.3 (37.9–80.7)	32.3 (23.0–45.3)	48.4 (38.1–61.4)	35.3 (28.2–44.1)
AUC(0–τ) ratio†		1.27 (1.00–1.60)	1.37 (1.05–1.78)		1.50 (1.27–1.77)	0.874 (0.712–1.07)	1.31 (1.09–1.57)	0.954 (0.802–1.13)
Cmax* (μg/mL)	5.06 (4.82–5.32)	7.15 (5.05–10.1)	6.52 (4.47–9.51)	5.62 (5.35–5.92)	8.66 (6.08–12.3)	4.34 (3.16–5.96)	6.40 (5.02–8.15)	4.93 (3.83–6.34)
Cmax ratio†		1.41 (1.13–1.77)	1.29 (1.00–1.66)		1.54 (1.30–1.82)	0.772 (0.635–0.938)	1.14 (0.951–1.36)	0.876 (0.737–1.04)
Cτ* (μg/mL)	0.291 (0.271–0.312) (n = 190)	0.552 (0.406–0.750) (n = 19)	0.701 (0.413–1.19)	2.17 (2.05–2.30) (n = 158)	3.39 (2.51–4.57) (n = 16)	2.24 (1.70–2.93)	2.42 (1.90–3.07) (n = 23)	2.01 (1.74–2.32) (n = 40)
Cτ ratio†		1.90 (1.51–2.38)	2.41 (1.77–3.28)		1.56 (1.28–1.90)	1.03 (0.831–1.28)	1.12 (0.943–1.32)	0.926 (0.811–1.06)
CL/F* (mL/min/kg)	15.7 (14.9–16.4)	19.3 (13.2–28.2)	23.4 (14.9–36.8)	3.52 (3.33–3.71) (n = 157)	6.06 (4.12–8.91)	6.48 (4.68–8.98)	5.27 (4.16–6.68)	5.33 (4.23–6.68)
CL/F ratio†		1.23 (0.987–1.54)	1.49 (1.16–1.92)		1.72 (1.45–2.05)	1.84 (1.49–2.28)	1.50 (1.24–1.81)	1.52 (1.27–1.82)
CL/F* (mL/min)	1137 (1079–1197)	269 (193–376)	330 (203–538)	270 (257–284)	91.2 (60.0–139)	195 (136–279)	149 (104–214)	284 (227–354)
CL/F ratio†		0.237 (0.187–0.300)	0.290 (0.223–0.378)		0.338 (0.280–0.407)	0.721 (0.574–0.906)	0.553 (0.453–0.675)	1.05 (0.866–1.27)

*Geometric mean (95% confidence interval).
†Geometric least squares mean ratio (90% confidence interval).
CL/F indicates apparent clearance.

raised total cholesterol or raised low density lipoprotein cholesterol in the FPV group.

HIV-1 RNA and CD4+ Cell Responses

In the snapshot analysis, the response at week 48 was higher among the ART-naïve subjects (83%) than PI-naïve/NRTI-experienced subjects (65%) and PI-experienced subjects (48%) within the FPV/RTV treatment group and subjects within the FPV treatment group (60%) (see Fig., Supplemental Digital Content 5, http://links.lww.com/INF/B640). The majority of nonresponders were classified as such because they did not achieve viral suppression <400 copies/mL at week 48 (n = 15) or changed their background ART (n = 13).

Consistent with a higher proportion of PI-naïve subjects, the 2- to <6-year olds in the FPV/RTV group had the largest proportion of subjects (74%, 14/19) with HIV-1 RNA levels <400 copies/mL at week 48 compared with the 6- to <12-year-old and 12- to 18-year-old age groups (53%, 16/30, and 63%, 25/40, respectively).

At week 48, the median CD4+ cell count changes from baseline were 340 cells/mm^3 in the FPV group and 190 cells/mm^3 in the FPV/RTV group, whereas the median percentage CD4+ cell count change from baseline was 8% in both groups. In the FPV/RTV group, the median CD4+ cell count change in 2- to <6-, 6- to <12- and 12- to 18-year olds was 174, 210 and 140 cells/mm^3, respectively; the respective percentage CD4+ cell count change was 10%, 7% and 7%.

TABLE 3. All AEs Occurring in More Than 10% of Subjects Overall

Any Adverse Event	FPV	FPV/RTV			Total
	2 to <6 yr (N = 20)	2 to <6 yr (N = 19)	6 to <12 yr (N = 30)	12 to 18 yr (N = 40)	2 to 18 yr (N = 109)
Number of subjects experiencing at least 1 treatment-emergent AE	19 (95)	18 (95)	27 (90)	38 (95)	102 (94)
Vomiting	12 (60)	5 (26)	15 (50)	8 (20)	40 (37)
Cough	1 (5)	8 (42)	10 (33)	15 (38)	34 (31)
Diarrhea	2 (10)	4 (21)	9 (30)	13 (33)	28 (26)
Upper respiratory tract infection	3 (15)	5 (26)	7 (23)	8 (20)	23 (21)
Pyrexia	1 (5)	2 (11)	11 (37)	7 (18)	21 (19)
Nasopharyngitis	1 (5)	1 (5)	10 (33)	5 (13)	17 (16)
Respiratory tract infection	13 (65)	1 (5)	1 (3)	2 (5)	17 (16)
Rhinitis	2 (10)	9 (47)	1 (3)	5 (13)	17 (16)
Bronchitis	3 (15)	1 (5)	5 (17)	6 (15)	15 (14)
Ear infection	3 (15)	1 (5)	7 (23)	3 (8)	14 (13)
Headache	0	1 (5)	6 (20)	7 (18)	14 (13)
Rash	0	4 (21)	6 (20)	4 (10)	14 (13)

Virology

Overall, 25 subjects (23%) met VF criteria. Of these, 21% (19/89) subjects were receiving FPV/RTV and 30% (6/20) were receiving FPV; 10 subjects failed to achieve plasma HIV-1 RNA suppression to <400 copies/mL by week 24, whereas 15 subjects experienced a confirmed rebound HIV-1 RNA to ≥400 copies/mL after achieving a plasma HIV-1 RNA of <400 copies/mL. The majority of these VF subjects (68%) were ART-experienced and 6 years or older (76%). All of the subjects with VF on FPV/RTV-containing regimens were 6 years or older. The majority of ART-experienced VF subjects (67%) had suboptimal treatment regimens at study start, that is, harbored viruses susceptible to <3 antiviral drugs in their baseline regimen (data not shown). Paired baseline and VF time point HIV-1 genotypic and phenotypic data were obtained for 15 of 25 VF subjects. Six VF subjects had virus with treatment-emergent NRTI and/or PI mutations resulting in treatment-emergent reductions in drug susceptibility. Virus from 3 FPV-treated subjects selected NRTI mutations (M184V); 2 also selected PI mutations (major PI mutations included M46M/L, I 50I/V, I54I/L, Q58Q/E). Virus from 3 FPV/RTV-treated, ART-experienced subjects selected treatment-emergent PI and/or NRTI mutations, including major PI mutations M46M/I, I50I/V, M54M/I or M/I/V (2 subjects) and NRTI mutations M184V and T215Y (2 subjects).[17] Treatment-emergent reductions in FPV susceptibility were observed in virus from only 4 subjects (2 receiving FPV and 2 receiving FPV/RTV-containing regimens) at VF.[17] A seventh ART-experienced subject (of the 15 VFs with paired genotype) had virus with only treatment-emergent reductions in drug susceptibility (to didanosine).

DISCUSSION

The FPV and FPV/RTV regimens administered in this study achieved plasma APV exposures similar to or higher than plasma APV exposures achieved in adults receiving standard regimens of FPV 1400 mg BID or FPV/RTV 700/100 mg BID. Plasma APV exposures following FPV/RTV 23/3 mg/kg BID in 2- to <6-year-old subjects were higher than following 18/3 mg/kg or 700/100 mg in older children and were ~50% higher than those observed in adults. Despite higher plasma APV exposures, there was no obvious difference in the safety profile in the 2- to <6-year-age group compared with the 2 older age groups.

Vomiting and neutropenia occurred more frequently in children than in adults.[13,18] Vomiting was more common in children in the FPV group, perhaps due to the larger volumes of FPV suspension or the younger age of this cohort. Grade 3/4 neutropenia was reported in 15% of children, although the late onset and the use of concomitant medications that may be associated with neutropenia suggest that it is unlikely to be FPV related. The proportion of subjects achieving HIV-1 RNA <400 copies/mL at week 48 ranged from 48% among PI-experienced to 83% among ART-naïve children; this compares to 66% to 73% in ART-naïve adults in the NEAT, SOLO and KLEAN studies and 58% in ART-experienced adults in the CONTEXT study indicating an adequate antiviral response when considering that this pediatric population included PI-naïve and PI-experienced subjects.[18,19]

Treatment-emergent FPV mutations and reduced viral susceptibility to FPV were detected in virus from 4 VF subjects, and the mutational profile was similar to that observed in adults. FPV and darunavir can select for a predominantly overlapping set of viral resistance-associated mutations and treatment-emergent major PI mutations associated with FPV or darunavir resistance were observed in virus from 4 subjects; however, no virus from VF subjects developed reduced susceptibility to darunavir.

Two small epidemiologic surveys on pediatric FPV/RTV use in routine clinical practice have concluded that FPV/RTV treatment had shown sustained antiviral response and immunologic improvement in ART-naïve and -experienced patients and did not identify new safety concerns.[20–22]

The safety and antiviral activity of FPV and FPV/RTV in APV29005 were not directly compared with other PIs, and cross-study comparisons are difficult because of differences in study designs and analyses. Virologic and immunologic responses in this study appear comparable to those seen with the lopinavir (LPV)/RTV liquid formulation in a cohort of children 6 months to 12 years of age.[23] After 48 weeks of therapy with LPV/RTV, 88% of ART-naïve, 84% of PI-naïve/NRTI-experienced and 58% of PI-experienced/NRTI-experienced subjects had HIV-1 RNA <400 copies/mL using an ITT (missing = failure) analysis while the respective numbers in the FPV study were 83%, 65% and 48% using the snapshot analysis. Unlike in APV29005, subjects with prior non-nucleoside reverse transcriptase inhibitor–containing ART were excluded in the LPV/RTV study. Mean increases in CD4+ cell count percentages were similar in APV29005 and the LPV/RTV study.

In the Pediatric AIDS Clinical Trial Group (PACTG) 1020A study, evaluating the efficacy of once-daily RTV-boosted atazanavir also using an ITT (missing = failure) analysis, the response rates for HIV RNA <400 copies/mL at week 48 were 88% (14/16) and 32% (8/25) in ART-naïve and -experienced, 6- to <18-year olds, respectively.[24] In the DELPHI study, 59% of mostly PI-experienced children aged 6 to 17 years and treated with RTV-boosted darunavir achieved a viral load of <400 copies/mL at week 48 (time to loss of virologic response).[25]

In summary, data from this study suggest that FPV-containing regimens administered to HIV-1–infected PI-naïve and PI-experienced children 2 to 18 years of age was generally well-tolerated with no major differences in the safety profile across the wide age range studied and provided sustained antiviral activity over 48 weeks, with plasma APV exposures comparable with or higher than adults. Although unboosted FPV is not a first-line therapy in children and requires larger dosing volumes than boosted regimens, it can still be an option for children with resistance to non-nucleoside reverse transcriptase inhibitors or for those children who require a PI but cannot tolerate RTV boosting.

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