OPEN

Pharmacokinetics, Safety and Antiviral Activity of Fosamprenavir/Ritonavir-containing Regimens in HIV-infected Children Aged 4 Weeks to 2 Years—48-week Study Data

Mark Cotton, MMed, Haseena Cassim, MD,† Noris Pavía-Ruz, MD,‡ Harmony P. Garges, MD,§ Teodora Perger, MD,¶ Susan L. Ford, PharmD,§ Mary Beth Wire, PharmD,§ Naomi Givens, MSc,¶ Lisa L. Ross, MS,§ Yu Lou, MS,§ Jörg Sievers, DPhil,¶ and Katharine Cheng, MD¶*

Background: Pharmacokinetics, safety and antiviral activity of fosamprenavir (FPV) with ritonavir (RTV) twice daily were evaluated in HIV-1–infected infants and children 4 weeks to <2 years over 48 weeks.

Methods: Results from intensive pharmacokinetic sampling of subjects enrolled in single dose visits was used to determine individualized dosing for the first 6–10 subjects in each of 2 cohorts (4 weeks to <6 months, 6 months to <2 years); steady state pharmacokinetic data were then used to select the dosage regimen for the remaining subjects recruited to the cohort. Intensive pharmacokinetic sampling was performed at week 2 or 8; predose samples were collected every 4–12 weeks thereafter. Safety and plasma HIV-1 RNA were monitored every 4–12 weeks.

Results: Fifty-nine subjects received study medication. FPV 45 mg/kg boosted with RTV 7 to 10 mg/kg BID achieved average plasma amprenavir area under curve(0–τ) values 26% to 28% lower and Cmax similar to historical adult data for FPV/RTV 700/100 mg BID; amprenavir Cτ values were lower in the subjects <6 months of age. At week 48, 35 of 54 (65%) subjects had achieved plasma HIV-1 RNA <400 copies/mL and 33 of 54 (61%) had plasma HIV-1 RNA values <50 copies/mL. The most common adverse events were diarrhea, upper respiratory tract infection, gastroenteritis and otitis media.

Conclusions: Final FPV/RTV dosing regimens achieved plasma amprenavir exposures comparable with those from regimens approved in adults, with the exception of trough exposures in the <6-month-old infants. The FPV/RTV regimens led to viral suppression in 61% of patients and were generally well tolerated.

Key Words: fosamprenavir, HIV-1, infants, children

(*Pediatr Infect Dis J* 2014;33:57–62)

Accepted for publication May 14, 2013.

From the *Department of Pediatrics and Child Health, Children's Infectious Diseases Clinical Research Unit, Stellenbosch University, Tygerberg; †Perinatal HIV Research Unit, Johannesburg, South Africa; ‡Universidad Nacional Autonoma de Mexico, Mexico City, Mexico; §GlaxoSmithKline, Research Triangle Park, NC; and ¶GlaxoSmithKline, Uxbridge, United Kingdom.

M.C. received support from a grant from ViiV Healthcare and payment for lectures, including service on speakers' bureaus, from Abbott Laboratories. H.P.G., T.P., S.L.F., M.B.W., N.G., L.L.R., Y.L., J.S. and K.C. are employees of GlaxoSmithKline.

This study is sponsored and funded by ViiV Healthcare; GlaxoSmithKline is responsible for implementing and managing all aspects of this study. The authors have no other funding or conflicts of interest to disclose.

Address for correspondence: Katharine Cheng, MD, GlaxoSmithKline, Stockley Park West, Uxbridge, UB11 1BT. E-mail: katharine.y.cheng@gsk.com.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/14/3301-0057
DOI: 10.1097/INF.0b013e3182a1123a

Fosamprenavir (FPV) is the phosphate ester prodrug of the protease inhibitor (PI) amprenavir (APV), developed to improve the delivery of APV to adults and children. The safety and efficacy of FPV has been established in adults in 3 phase III 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.[1–3] FPV and FPV/RTV BID regimens have been established in children 2 to 18 years of age.[4] This study, APV20002, evaluates the pharmacokinetics (PK), safety, tolerability and antiviral activity of FPV oral suspension administered with RTV in a BID regimen to PI-naïve and PI-experienced subjects 4 weeks to <2 years of age. Recruitment commenced in October 2003 and completed in July 2010. The study is ongoing, and the 48-week data (data cutoff July 5, 2011) presented here include data up to and including the last subject reaching the week 48 visit.

METHODS

Study Design

This international, 48-week, phase II, open-label, 2-cohort, multicenter study enrolled HIV-1–infected subjects, 4 weeks to <2 years of age, across 7 sites in South Africa, Mexico, Argentina and Portugal. The primary objective was to identify the FPV/RTV BID regimens that delivered plasma APV exposures comparable with those already proven to be effective in adults and to evaluate the safety, tolerability and antiviral response of these regimens over 48 weeks in 2 cohorts: cohort 1 (6 months to <2 years) and cohort 2 (4 weeks to <6 months). Subjects have been allowed to continue receiving FPV beyond week 48 until local approval in the relevant age cohort and commercial supplies are available or until they no longer derive clinical benefit.

The study was 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 performing any study-specific procedures.

Study Population

Male and female subjects (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 enrolment and were either PI-naïve (defined as having received <1 week of any PI regardless of length of therapy with nucleoside reverse transcriptase inhibitors [NRTIs] and/or non-nucleoside reverse transcriptase inhibitors [NNRTIs], including completely antiretroviral therapy [ART]-naïve) or PI-experienced (defined as having prior experience with no more than 3 PIs).

Subjects were excluded from participation if they had a serious medical condition that might compromise safety, had previously received APV, had received therapy with NNRTIs in the 14 days before study drug administration or had within 28 days

of commencing the study, grade 3 or 4 alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) using the Division of AIDS Toxicity Tables for Grading Severity of Pediatric Adverse Experiences[5,6] or if they had 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.

Drugs and Doses

Approximately 10 subjects enrolled in each cohort underwent single dose PK visits to select individualized repeat dosage regimens. Planned initial single doses for PK evaluation for both cohorts were FPV 30 mg/kg and FPV/RTV 30/6 mg/kg, consistent with doses evaluated in older children.[7] Subsequently, evaluation of single dose unboosted FPV was stopped due to high volume requirements and a higher single dose of FPV/RTV 45/7 mg/kg was implemented for PK evaluation in the 4 weeks to <6 months age cohort based on data from the older 6 months to <2 years group. Individualized FPV/RTV BID repeat dosage regimens were initiated within 2–6 weeks of the single dose PK visit; changes to repeat dosage regimens were allowed based on repeat dose PK data. Repeat dose data from subjects receiving individualized regimens was used to select FPV/RTV BID repeat dosage regimens for subsequently enrolled subjects; 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 is provided (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B630, showing range of individualized doses and revised regimens).

GlaxoSmithKline provided FPV/RTV BID and offered subjects abacavir oral solution (20 mg/mL) and lamivudine oral solution (10 mg/mL) as optional background NRTI therapy (if required). FPV was administered as 50 mg/mL oral suspension, and RTV, sourced locally, was given as an 80 mg/mL oral solution. Other NRTIs were obtained on prescription.

Study Evaluations

Subjects were evaluated at screening and baseline visits and at weeks 2, 4, 8, 12, 16, 24, 36 and 48, and every 12 weeks thereafter. Subjects completed a follow-up visit 4 weeks after discontinuation of study medication.

All subjects underwent PK sampling following repeat dose administration including intensive PK sampling (0, 1, 2, 4, 6, 8 and 12 hours [optional] postdose) at either week 2 or week 8 and predose sampling at all other visits. Additional predose PK sampling was added at 2–3 visits during the study to determine unbound APV concentrations to better evaluate whether subjects <2 years old achieved similar unbound APV concentrations even if total APV concentrations were lower than historical adult values.

Safety evaluations including hematology, clinical chemistry (including lipids) and adverse events (AEs) were conducted at every visit; lipid evaluation samples were not collected under fasting conditions due the young age of the subjects. The Division of AIDS Toxicity Tables were used for severity grading.[5,6]

Antiviral 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 analysis was attempted at the baseline and virologic failure (VF) time point for any subject meeting the analysis plan definition of VF.

Statistical Analysis

As this was a noncomparative study, no formal statistical hypothesis testing was performed. An initial sample size of 24 subjects (12 per age cohort) was considered appropriate to allow an accurate description of plasma APV PK, safety and tolerability of FPV/RTV BID. Twelve subjects providing plasma APV PK data for each cohort and regimen were predicted to give a 95% confidence interval with 76% and 130% of the geometric mean estimate of area under the concentration–time curve over a dosing interval (AUC[0–τ]). When a dose modification was made, further subjects were recruited to the cohort to achieve a minimum of 8 subjects providing steady state PK data on the revised dose.

The primary endpoints of the study were plasma total APV AUC(0–τ), maximum concentration (Cmax), concentration at the end of a dosing interval (Cτ), apparent clearance (CL/F) and plasma unbound APV Cτ, assessment of the incidence, nature and severity of AEs, laboratory abnormalities and treatment-limiting toxicities and the proportion of subjects discontinuing study medication due to AEs. Secondary endpoints included plasma RTV AUC(0–τ), Cmax, Cτ, CL/F and plasma FPV prodrug concentrations, the proportion of subjects with HIV-1 RNA levels <400 copies/mL, change from baseline in plasma HIV-1 RNA and in the percentage CD4+ lymphocytes at each study visit and incidence of viral resistance.

Snapshot and "observed" analyses were used to summarize the proportion of subjects achieving plasma HIV-RNA concentrations <400 and <50 copies/mL at week 48. For the snapshot analysis, subjects with missing data in the window of interest were considered nonresponders. Subjects who switched or added background ART were also considered nonresponders unless there was documented evidence of toxicity and the change was made before the first on-treatment viral load (VL) assessment at week 2. Otherwise, responder or nonresponder classification was determined by the last available HIV-1 RNA assessment while the subject was on-treatment within the window of the visit of interest.

Pharmacokinetic Analysis

PK calculations were based on actual dose and sample collection times recorded. 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 CL/F. Data from all predose concentrations collected at periodic visits were included in the overall APV and RTV Cτ PK summaries, provided the samples were collected within 8 to 16 hours of the previous dose.

Plasma APV and RTV PK parameters were summarized by dose and age cohort when sample size was sufficient. Data were included in the PK summary when the actual regimen was within 10% of the nominal regimen. Subjects were assigned to age cohorts based on age at PK sampling (not baseline age). PK data were plotted by actual dosage regimen and age group. Plasma APV and RTV PK parameters were compared with historical adult data from159 healthy adults receiving FPV/RTV 700/100 mg twice daily. 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.

Virology Analysis

VF criteria included failure to achieve 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.[8]

TABLE 1. Demographic and Baseline Characteristics by Age Cohort (ITT-E Population)

	4 wk to <6 mo N = 26	6 mo to <2 yr N = 28	Total N = 54
Age, (mo) median (range)	3 (2, 5)	13 (6, 24)	16 (2, 24)
Weight, (kg) median (range)	5.4 (3.2, 7.8)	8.2 (4.9, 11.1)	6.4 (3.2, 11.1)
Sex, n (%)			
Female	13 (50)	18 (64)	31 (57)
Male	13 (50)	10 (36)	23 (43)
Ethnicity, n (%)			
Hispanic or Latino	0	9 (32)	9 (16)
Non-Hispanic or Latino	26 (100)	19 (68)	45 (83)
Race, n (%)			
Black	25 (96)	19 (68)	44 (81)
White/Caucasian	1 (4)	1 (4)	2 (4)
Other (American Indian)	0	8 (29)	8 (15)
Baseline HIV-1 RNA			
Median plasma HIV-1 RNA log10 copies/mL, (IQR)	5.80 (5.17, 6.30)	5.51 (4.81, 5.76)	5.60 (5.00, 6.15)
HIV-1 RNA copies/mL, n (%)			
<400	1 (4)	0	1 (2)
400 to <5000	3 (12)	2 (7)	5 (9)
5000 to <100,000	2 (8)	6 (21)	8 (15)
100,000 to <250,000	1 (4)	4 (14)	5 (9)
250,000 to <500,000	4 (15)	8 (29)	12 (22)
≥500,000	15 (58)	8 (29)	23 (43)
Baseline CD4+ cell counts			
Median CD4+ cells/mm^3, (IQR)	1378 (950, 1690)	1120 (874, 1828)	1235 (937, 1795)
Median % CD4+ cells, (IQR)	27 (20, 36)	25 (18, 21)	26 (18, 34)
% CD4+ cells, n (%)			
<15	3 (12)	4 (14)	7 (13)
15 to <25	8 (31)	10 (36)	18 (33)
≥25%	12 (46)	14 (50)	26 (48)

IQR, interquartile range.

RESULTS

Study Population

Fifty-nine subjects received ≥1 dose of study medication (safety population); five subjects discontinued after the single dose visit(s). Of the 54 subjects who received FPV/RTV BID (intent-to-treat–exposed [ITT-E] population), 28 were in the 6 months to <2 years age cohort and 26 were in the 4 weeks to <6 months age cohort (age range at baseline 2–24 months, ie, 1 subject enrolled at aged 24 months). All acquired HIV-1 perinatally. Enrolled subjects were from South Africa (45), Mexico (8), Argentina (1) and Portugal (1). Overall, there were more females (57%) than males (43%) (Table 1). The majority of subjects (81%) were black. Median baseline plasma HIV-1 RNA (log_{10} copies/mL) was high in both age cohorts: 5.80 in the 4 weeks to <6 months age cohort and 5.51 in the 6 months to <2 years age cohort.

Thirty-eight of the 54 subjects (70%) were ART-experienced. The majority of these (29/38, 76%) had received 1 day of nevirapine and/or 4 to 28 days of zidovudine, presumably as prophylaxis for mother-to-child transmission. Thirteen percent (5/18) of subjects, all in the 6 months to <2 years age cohort, had received PIs in combination with other ART for 3–15 months before entering the study. Four additional subjects had received treatment with NRTIs with or without nevirapine for >28 days; 3 were in the 6 month to <2 year age cohort.

The median time of exposure to FPV/RTV BID was 540 days with 42 (78%) subjects receiving study medication for >48 weeks and 27 (50%) subjects for >96 weeks.

Twenty-nine subjects discontinued treatment; 15 (28%) subjects discontinued treatment ≤48 weeks and 14 discontinued after week 48 (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B631). Reasons for discontinuation included AEs (n = 3 ≤ week 48, n = 1 after week 48) and insufficient VL response (n = 2 ≤ week 48, n = 1 after week 48) (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B631, showing disposition of subjects).

Pharmacokinetics

Subjects in the 6 months to <2 years age cohort who received FPV/RTV 45/7 mg/kg BID achieved 26% lower APV AUC(0–τ) and equivalent Cmax and Cτ values compared with the historical adult population receiving FPV/RTV 700/100 mg BID (Table 2). The FPV/RTV 60/7 mg/kg BID regimen in the 6 months to <2 years age cohort delivered higher plasma APV exposure than FPV/RTV 45/7 mg/kg BID in the same age cohort and than historical adult data (Table 2 and Fig., Supplemental Digital Content 3, http://links.lww.com/INF/B632, showing plasma APV pharmacokinetic parameters compared with historical adults).

Subjects in the 4 weeks to <6 months age cohort who received FPV/RTV 45/10 mg/kg BID achieved 28% lower APV AUC(0–τ), 11% higher Cmax and 60% lower Cτ values than the historical adult population receiving FPV/RTV 700/100 mg BID (Table 2). Weight-based plasma APV CL/F (mL/min/kg) values were similar between the age cohorts and were 6.5-fold the values observed in the historical adult population; unadjusted APV CL/F (mL/min) values were 30% to 50% lower than values observed in adults (not shown). Overall, the median percentage unbound APV Cτ in pediatric subjects was 6.4%.

Subjects in the 6 months to <2 years age cohort who received FPV with RTV 7 mg/kg BID had 63% higher plasma RTV AUC(0–τ), 62% higher Cmax and 80% higher Cτ values compared with the historical adult population receiving FPV/RTV 700/100 mg BID (see Table, Supplemental Digital Content 4, http://links.lww.com/INF/B633, showing plasma RTV pharmacokinetic parameters).

Subjects in the 4 weeks to <6 months age cohort who received FPV with RTV 10 mg/kg BID had 2.86-fold higher plasma RTV AUC(0–τ), 2.46-fold higher Cmax and 36% higher Cτ values compared with the historical adult population receiving FPV/RTV 700/100 mg BID (see Table, Supplemental Digital Content 4, http://

TABLE 2. Summary of Steady State Plasma Amprenavir Pharmacokinetic Parameters in Children 4 Weeks to <2 Years of Age and Statistical Comparisons to Historical Adult Values

Plasma APV PK Parameter	Historical Healthy Adult	6 mo to <2 yr				4 wk to <6 mo	
	700/100 mg BID* N = 159	FPV/RTV 45/7 mg/kg BID n = 10		FPV/RTV 60/7 mg/kg BID n = 8		FPV/RTV 45/10 mg/kg BID n = 9	
		Geometric Mean (95% CI)	GLSM Ratio (90% CI)	Geometric Mean (95% CI)	GLSM Ratio (90% CI)	Geometric Mean (95% CI)	GLSM Ratio (90% CI)
AUC(0–τ) (h·μg/mL)	37.0 (35.1–38.9) (n = 158)	27.5 (14.5–52.1)	0.744 (0.568–0.975)	48.4 (12.9–181)	1.31 (0.970–1.77)	26.6 (15.2–46.8)	0.720 (0.542–0.957)
Cmax (μg/mL)	5.62 (5.35–5.92)	5.84 (3.35–10.2)	1.04 (0.807–1.34)	10.4 (3.64–30.0) (n = 9)	1.86 (1.42–2.42)	6.25 (3.82–10.2)	1.11 (0.853–1.45)
Cτ (μg/mL)	2.17 (2.05–2.30)	2.17 (1.69–2.80) (n = 29)	1.00 (0.833–1.21)	2.81 (1.69–4.67) (n = 12)	1.30 (0.986–1.70)	0.860 (0.500–1.48) (n = 11)	0.397 (0.298–0.528)
CL/F (mL/min/kg)	3.52 (3.33–3.71) (n = 157)	22.8 (12.0–43.1)	6.47 (4.67–8.97)	17.8 (4.75–66.7)	5.06 (3.52–7.27)	22.9 (12.9–40.6)	6.51 (4.62–9.17)

*Geometric mean (95% CI).
CI indicates confidence interval; GLSM, geometric least squares mean.

links.lww.com/INF/B633). Across the 2 age cohorts, weight-based plasma RTV CL/F (mL/min/kg) values were on average 2.5- to 3.1-fold the values observed in the historical adult population; unadjusted RTV CL/F (mL/min) values were 75% to 80% lower than values observed in adults (not shown).

FPV was rapidly and extensively converted to APV. Plasma FPV prodrug concentrations were undetectable in the majority (88%) of samples; quantifiable FPV prodrug concentrations were low, ranging from 0.005 μg/mL to 0.286 μg/mL, with the exception of 1 sample with a FPV concentration of 2.81 μg/mL.

Safety

Overall, 92% (54/59) of subjects reported at least 1 AE (29/30, 97% in the 6 months to <2 years age cohort, and 25/29, 86% in the 4 weeks to <6 months age cohort). AEs occurring in more than 10% subjects overall are listed in Table 3. Rash-type events (including dermatitis, allergic dermatitis, urticaria and cellulitis) were reported by 15% subjects overall although none were considered to be drug related.

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

	FPV/RTV BID N = 59 n (%)
Subjects reporting at least 1 treatment-emergent AE	54 (92)
Diarrhea	32 (54)
Gastroenteritis	21 (36)
Upper respiratory tract infection	21 (36)
Otitis media*	21 (36)
Nasopharyngitis	17 (29)
Pharyngitis	17 (29)
Rhinitis	15 (25)
Vomiting	13 (22)
Blood cholesterol increased	11 (19)
Conjunctivitis	10 (17)
Cough	10 (17)
Tonsillitis	10 (17)
Bronchitis	7 (12)
Dermatitis diaper	7 (12)
Impetigo	7 (12)
Seborrheic dermatitis	7 (12)

*The terms otitis media and acute otitis media have been combined.

Nineteen subjects (32%) reported severe or grade 3/4 treatment-emergent AEs, with bronchopneumonia (n = 4), gastroenteritis (n = 4), blood creatine phosphokinase increased (n = 2), hypertension (n = 2), neutropenia (n = 2), pneumonia (n = 2) and urinary tract infection (n = 2) being reported by more than 1 subject. The majority of grade 3/4 AEs were considered not drug related with the exception of single cases of thrombocytopenia, febrile convulsion and transaminase increased (all grade 3) and 1 report of gastroenteritis (grade 4).

There were 21 (36%) drug-related AEs, the most common being increases in blood cholesterol (14%, 8/59), increases in blood triglycerides and diarrhea (each 7%, 4/59). The majority of drug-related AEs were grade 1 or grade 2.

Three deaths were reported during the study; 2 were not considered drug related. One infant died following an acute abdominal disorder 11 days after having received single doses of FPV and FPV/RTV; 1 infant died of septicemia. The third death occurred in an infant following acute gastroenteritis (possibly drug related) and herbal medicine poisoning (not considered study drug related). A further 19 subjects reported serious AEs; 2 were considered possibly related to study medication by the investigator (febrile seizure, transaminase increased); the subject with "febrile seizure" also had pharyngitis, a possible source of infection.

Ten subjects had treatment-emergent grade 3/4 laboratory abnormalities (see Table, Supplemental Digital Content 5, http://links.lww.com/INF/B634, showing subjects with grade 3/4 laboratory abnormalities).

Grade 3 ALT was reported for 3 subjects who were asymptomatic and had no associated rise in bilirubin levels. In 2 cases, all antiretrovirals were interrupted which resulted in improved ALT levels; when ART (including FPV/RTV) was reintroduced, ALT levels remained normal. The third subject had a long time to onset (week 108) for grade 3 ALT and grade 2 AST, which both worsened to grade 4 and were reported as an serious AE. The subject remained asymptomatic and all antiretrovirals were interrupted. Urine culture revealed *Proteus mirabilis* and following treatment with cefuroxime, transaminases improved and ART, including FPV, was reintroduced without any additional rise in ALT/AST.

There were no grade 3/4 cholesterol abnormalities. The median baseline total cholesterol was 2.8 mmol/L; the median increase from baseline at week 48 was 1.5 mmol/L, manifested by median increases in high density lipoprotein and low density lipoprotein cholesterol. The median baseline triglyceride was 1.7 mmol/L with little change in median triglyceride values up to week 48 (−0.3 mmol/L).

Six subjects had grade 3/4 hematology abnormalities, 1 subject with grade 3 hemoglobin, 4 subjects with grade 3 neutropenia and 1 subject with grade 4 neutropenia. All 5 neutropenia cases resolved with continued FPV treatment. In 3 subjects, neutropenia occurred at week 4 (2 of these subjects were taking concomitant medications associated with neutropenia). The fourth subject developed grade 3 neutropenia at week 84. The fifth subject had an *Escherichia coli* urinary tract infection considered to be the cause of the grade 4 neutropenia.

Antiviral Response

At week 48, the median HIV-1 RNA ($\log_{10}$ copies/mL) was below the limit of detection in both age cohorts; the proportion of subjects achieving HIV-1 RNA <400 copies/mL was 65%, and 61% achieving HIV-1 RNA< 50 copies/mL. In the Snapshot analysis, the proportion of subjects achieving HIV-1 RNA <400 copies/mL up to week 36 was similar between age cohorts, whereas at week 48 the proportions were 71% (20/28) in the 6 months to <2 years age cohort and 58% (15/26) in the 4 weeks to <6 months age cohort (see Fig., Supplemental Digital Content 6, http://links.lww.com/INF/B635, showing virologic response). The proportion of subjects with HIV-1 RNA <50 copies/mL at week 48 was similar between the 2 age cohorts (64% [18/28] in the 6 months to <2 years age cohort and 58% [15/26] in the 4 weeks to <6 months age cohort). Median CD4+ cell percentages in each age cohort improved, with a median change from baseline in both age cohorts of +5%.

Virology

Overall, 9 subjects (17%) met VF criteria; 7 of these 9 were ART-experienced, and 3 had extensive prior ART exposure. Of the 9 subjects, 8 failed to achieve virologic suppression to <400 copies/mL by week 24; the ninth subject experienced viral rebound. Paired viral genotypes and phenotypes were obtained at baseline and VF from 7 subjects. Protease and reverse transcriptase resistance-associated mutations detected at baseline were analyzed in virus from all subjects with available genotypes (N = 18/54). Only minor PI and NNRTI mutations were detected in virus from ART-naïve subjects. NRTI mutations were detected in virus from 5/12 therapy-experienced subjects, including major NNRTI mutations in 3/12 viral isolates and major PI mutations in 1/12 viral isolates. Virus from 2 subjects developed any major treatment-emergent drug resistance-associated mutations or reduced drug susceptibility, including a treatment-emergent reverse transcriptase mutation M184M/V in virus from 1 antiretroviral-naïve subject (this virus also developed reduced susceptibility to lamivudine and emtricitabine). Virus from a second therapy-experienced subject with multiple baseline mutations developed reduced susceptibility to FPV at failure without selecting any major protease mutation. Virus from the third subject, who was previously antiretroviral-naïve, selected a single treatment-emergent minor mutation (PI mutation L10I), which had no impact on drug susceptibility. Of the mutations associated with darunavir resistance (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V), only the minor mutation L33F (or an L33L/F mixture) was treatment-emergent at VF in virus from 2 subjects.

DISCUSSION

The dosage regimen of FPV 45 mg/kg with RTV 7 to 10 mg/kg BID achieved average plasma APV AUC(0–τ) values 26% to 28% lower and Cmax similar to historical adult data for FPV/RTV 700/100 mg BID. Despite consistent plasma APV AUC(0-τ) and Cmax values across the 2 age cohorts, subjects in the 6 months to <2 years age cohort achieved plasma APV Cτ values similar to historical adult values whereas younger infants, in the 4 weeks to <6 months age cohort, achieved 60% lower plasma APV Cτ values. The 50 mg/mL concentration of FPV suspension constrains the upper limit of tolerable dosing volumes, and dosages above 45 mg/kg were not studied broadly in this age group and high dosing volumes precluded evaluation of unboosted doses of FPV. Overall, the median percentage unbound APV Cτ in pediatric subjects was 6.4%, similar to that observed in HIV-infected adult subjects[9] suggesting that lower total APV concentrations would be associated with lower unbound concentrations available to interact with HIV protease.

Although younger infants had lower plasma APV Cτ values, the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48 was similar in the 2 age groups. The lower APV Cτ levels increased to 88% of adult targets (1.92 μg/mL, n = 15) when these younger infants continued to receive FPV/RTV 45/10 mg/kg BID after reaching 6 months of age. Therefore, in this study, the initial lower APV exposures had little impact on longer term VL suppression in infants <6 months of age.

Plasma RTV exposure was higher in infants and children than in the historical adult population, particularly in the 4 weeks to <6 months age cohort who received the highest studied RTV boost dose of 10 mg/kg BID. Given that RTV AUC and Cmax are well above concentrations associated with maximal boost effect in adults[10,11] and that weight-adjusted RTV oral clearance (CL/F/kg) between both age groups is comparable, an RTV boosting dose of 7 mg/kg may be appropriate in subjects 4 weeks to <6 months of age.

Although the lowest age limit of protocol eligibility was 4 weeks old, 4 infants were ≤12 weeks at baseline. Therefore, our data are limited in infants ≤3 months of age. However, given similarities in hepatic CYP3A enzyme maturation, extrapolation of data to 1-month-old infants is possible. APV is eliminated primarily by CYP3A metabolism and hepatic CYP3A activity as a fraction of adult activity plateaus after 20 days.[12] In addition, scaling factors that relate infant microsomal protein, ontogeny and hepatic enzyme activity are described in age ranges, with 1- to 3-month olds given the same scaling factor values.[12] These similarities in enzyme maturation suggest that 1-month-old infants would have similar capacity to metabolize APV as 2- to 3-month-old infants, which supports extrapolation of data to infants born at term, of at least 4 weeks of age.[13]

The 48-week results from this study indicate that RTV-boosted FPV was generally well tolerated in infants and children. The AE profile was similar between the 2 age cohorts and consistent to that seen in older children and adults.[4,14] The most common AEs in this study reflect the most common illnesses experienced in young infants. The incidence of diarrhea and upper respiratory tract infections was higher in infants than in children 2 to 18 years of age.[14] The proportion of subjects (22/59, 37%) reporting at least 1 serious AE in this study could reflect the young age of the study population and the lower threshold for hospital admission in this age cohort. There were 4 cases of grade 3/4 neutropenia but the pattern, with resolution of the neutropenia with continued FPV treatment, suggests that these were unlikely to be FPV related. Raised transaminases and elevation of lipids are recognized to be associated with PI use, including FPV; in this study, the number of subjects with grade 3/4 ALT/AST was low (6%, 3/49). There were no reports of grade 3/4 lipid elevations. However, slight increases in serum cholesterol occurred, which were not unexpected given the known effect of PIs on cholesterol. Additionally, data from healthy infants show that cholesterol

rapidly rises from approximately 1.8 mmol/L at birth to between 2.6 and 3.9 mmol/L during the first few weeks of life; thereafter, levels slowly increase to an average of 4.1 to 4.3 mmol/L at 2 years of age. The small triglyceride level changes observed were consistent with another study that followed infants under 6 months for 96 weeks.[15]

There was a lower proportion of subjects achieving HIV-1 RNA levels <400 copies/mL in the 4 weeks to <6 months age cohort compared with the 6 months to <2 years age cohort (58%, 15/26, vs. 71%, 20/28), but the proportions achieving HIV-1 RNA levels <50 copies/mL were similar (58%, 15/26, vs. 64%, 18/28). Differences in antiviral responses should be interpreted with caution given the small number of subjects in each cohort.

The antiviral response in this study was comparable with that seen in APV29005, a study of FPV ± RTV in 2- to 18-year olds.[14] In APV29005, consistent with a higher proportion of PI-naïve subjects, 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).

The proportion of subjects achieving HIV-1 RNA <400 copies/mL was 65% in APV20002 and also comparable to the responses observed in ART-naïve adults in the NEAT, SOLO and KLEAN studies (66–73%) and in ART-experienced adults in the CONTEXT study (58%).[16,17]

Differences in study designs and analyses make cross-study comparisons with other PIs difficult. However, the efficacy rates observed in this study appear comparable with rates from a study of lopinavir/RTV in infants 14 days to <6 months of age (P1030): 71% of infants achieved a VL of <400 copies/mL at week 48 (ITT; discontinuation = failure) (6/10 infants 14 days to <6 weeks and 16/21 infants 6 weeks to <6 months).[15] Low lopinavir levels were observed at 2 weeks of therapy with the lowest exposures in infants <6 weeks of age.

In the Pediatric AIDS Clinical Trials Group P345 study, which evaluated RTV efficacy in combination with zidovudine and lamivudine in HIV-infected infants and children up to 2 years of age using an ITT (off-treatment = failure) analysis, the response rates for HIV RNA <400 copies/mL were 72% at week 16 and 36% by week 104.[18]

Median change from baseline at week 48 in relative (percentage) CD4+ cell counts in subjects in the 4 weeks to <6 months age cohort in this study and in subjects <6 months of age in the P1030 study were comparable (5% vs. 4%).[15] The respective increases in percentage CD4+ cell counts in the 6 months to <2 years age cohort in this study and in subjects 6 months to 12 years of age in lopinavir/RTV study 940 were 5% and 6–10% (depending on prior ART experience).[19]

Development of new major viral resistance-associated mutations at VF was rare, as was treatment-emergent reduced susceptibility. This low level of treatment-emergent resistance in the VF population suggests that VF criteria may have been more likely to have been met in this subset due to a lack of adherence rather than a lack of regimen potency.

In summary, data from this study show that, across the doses studied, FPV administered with RTV to HIV-1–infected infants and children <2 years of age was generally well tolerated and provided sustained antiviral activity over 48 weeks. Plasma APV exposures were comparable with adults in infants aged 6 months to <2 years; although trough APV exposures were lower in infants <6 months, the proportions of subjects achieving an undetectable VL at week 48 were similar in the 2 age cohorts. These study results are complementary to another study with FPV, APV29005, including children from 2 to <18 years of age and together provide data across the 4 weeks to 18 years pediatric age range.

ACKNOWLEDGMENTS

We thank the children who participated in the study, the children's families/caregivers, all investigators and study personnel. We would also like to acknowledge Nicole MacLeod for medical writing and editorial assistance given in the preparation of the article (funded by ViiV Healthcare).

REFERENCES

1. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT Study: A 48-week open-label study to compare the antiviral efficacy and safety of GW43908 versus nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients. *JAIDS*. 2004;35:22–32.
2. Gathe JC Jr, Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir /ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS*. 2004;18:1529–1537.
3. DeJesus E, Lamarca A, Sension M, et al. The Context Study: Efficacy and safety of GW433908/RTV in PI-experienced subjects with virological failure (24 week results). In: *10th Conference on Retroviruses and Opportunistic Infections (CROI)*, Boston, MA, February 10–14, 2003. Abstract 178.
4. Lexiva. *US Prescribing Information.* 2012.
5. DAIDS Toxicity Tables 1994. Tables for grading severity of pediatric adverse experiences (≤3 months of age and >3 months of age). Available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Pediatric_AEs_Under3MonthsAge_v02.pdf and http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Pediatric_AEs_Over3MonthsAge_v03.pdf. Accessed May 13, 2013.
6. DAIDS Toxicity Tables. Tables for grading severity of pediatric adverse experiences Version 1.0, December 2004. Division of AIDS, NIAID. Available at: http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/daidsaegradingtable.pdf. Accessed September 16, 2011.
7. Chadwick E, Borkowsky W, Fortuny C, et al. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to18 years (48-week interim data, Study APV20003). In: *14th Conference on Retroviruses and Opportunistic Infections (CROI) 2007.* Los Angeles, CA, February 25–28, 2007. Poster 719.
8. HIV Drug Resistance Mutations. Available at: http://www.iasusa.org/resistance_mutations/index.html. Accessed March 21, 2011.
9. Pérez-Elías MJ, Morellon ML, Ortega E, et al. Pharmacokinetics of fosamprenavir plus ritonavir in human immunodeficiency virus type 1-infected adult subjects with hepatic impairment. *Antimicrob Agents Chemother*. 2009;53:5185–5196.
10. Sale M, Sadler BM, Stein DS. Pharmacokinetic modeling and simulations of interaction of amprenavir and ritonavir. *Antimicrob Agents Chemother*. 2002;46:746–754.
11. Sadler BM, Piliero PJ, Preston SL, et al. Pharmacokinetics and safety of amprenavir and ritonavir following multiple-dose co-administration to healthy volunteers. *AIDS*. 2001;15:1009–1018.
12. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part II. *Clin Pharmacokinet*. 2002;41:1077–1094.
13. Kearns GL, Robinson PK, Wilson JT, et al.; Pediatric Pharmacology Research Unit Network. Cisapride disposition in neonates and infants: *in vivo* reflection of cytochrome P450 3A4 ontogeny. *Clin Pharmacol Ther*. 2003;74:312–325.
14. Voronin E, Fortuny C, Perez-Tamarit D, et al. Pharmacokinetics, safety and antiviral activity of fosamprenavir-containing regimens in HIV-infected 2 to 18 year-old children (48-week data, Study APV29005, a prospective, open-label, multi-centre, 48-week cohort study) [Abstract MOPE049]. In: *19th International AIDS Conference* (*IAC*). Washington, DC, July 22–27, 2012.
15. Chadwick EG, Yogev R, Alvero CG, et al.; International Pediatric Adolescent Clinical Trials Group (IMPAACT) P1030 Team. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS*. 2011;25:643–649.
16. Torres HA, Arduino RC. Fosamprenavir calcium plus ritonavir for HIV infection. *Expert Rev Anti Infect Ther*. 2007;5:349–363.
17. Eron J Jr, Yeni P, Gathe J Jr, et al.; KLEAN study team. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*. 2006;368:476–482.
18. Chadwick EG, Rodman JH, Britto P, et al.; PACTG Protocol 345 Team. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. 2005;24:793–800.
19. Sáez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2003;22:216–224.