Office of Clinical Pharmacology Review

NDA(s)	**21548/S28 (tablet) & 22116/S12 (oral suspension)**
Submission Date	**October 28, 2011**
Brand Name	**Lexiva®**
Generic Name	**Fosamprenavir calcium**
Reviewer	**Dionna Green, M.D.**
Pharmacometrics Reviewer	**Jeffry Florian, Ph.D**
Pharmacometrics Team Leader (Acting)	**Yaning Wang, Ph.D.**
OCP Team Leader (Acting)	**Shirley Seo, Ph.D.**
OCP Division	**DCP IV**
OND Division	**DAVP**
Sponsor	**ViiV Healthcare**
Relevant IND(s)	**52,849**
Submission Type; Code	**Pediatric supplement**
Review Type(s)	**Priority**
Currently Marketed Formulation(s)	**Tablet (700 mg); oral suspension (50 mg/mL)**
Approved Dosing Regimen(s)	**Therapy-naïve adults:** **FPV 1400 mg BID (without RTV)** **FPV/RTV 1400/200 mg QD** **FPV/RTV 1400/100 mg QD** **FPV/RTV 700/100 mg BID** **Therapy-experienced adults:** **FPV/RTV 700/100 mg BID** **Therapy-naïve peds:** **2 to <18 yrs: FPV 30 mg/kg BID (without RTV)** **Treatment-naïve and -experienced peds:** **6 to <18 yrs: FPV/RTV 18/3 mg/kg BID**
Proposed Dosing Regimen(s)	**PI-naïve and -experienced peds:** (b) (4)
Proposed Indication	**Treatment of HIV-1 infection (in combination with other antiretroviral agents) in pediatric patients ages 4 weeks to <6 years old**

Table of Contents

List of Tables:

List of Figures:

1 EXECUTIVE SUMMARY

Fosamprenavir calcium (FPV, Lexiva), the prodrug of amprenavir (APV), is an HIV-1 protease inhibitor currently approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and in certain portions of the pediatric population. FPV is commercially available as a tablet (700 mg strength) and as an oral suspension (50 mg/mL). FPV can be administered with and without concomitant ritonavir, another HIV-1 protease inhibitor that increases APV plasma concentration by inhibiting its metabolism.

Several FPV dosage regimens are approved for the adult HIV population (**Table 1)**. For the pediatric population, approved dosage regimens include twice daily (BID) administration of FPV without RTV in treatment-naïve children 2 years of age and older and BID administration of FPV co-administered with RTV in treatment-naïve or -experienced children 6 years of age and older (**Table 2)**. Currently, there is no approved dosing recommendation for a twice daily FPV regimen co-administered with RTV in HIV-infected children <6 years of age.

Table 1 – Approved Lexiva Dosage Regimens for Adults

Treatment-naïve Adults	Treatment-experienced Adults
FPV 1400 mg BID	FPV/RTV 700/100 mg BID
FPV/RTV 1400/200 mg QD	
FPV/RTV 1400/100 mg QD	
FPV/RTV 700/100 mg BID	

Table 2 – Approved Lexiva Dosage Regimens for Pediatrics

Age Group	FPV alone[a] (treatment-naïve patients)	FPV/RTV[a] (treatment-naïve and -experienced patients)
2 to 5 years	30 mg/kg BID[b]	NA
≥6 years	30 mg/kg BID[b]	18/3 mg/kg BID[c]

NA = Not approved

a. LEXIVA Oral Suspension should be administered with food in pediatric patients as was done in clinical studies.
b. Up to a maximum dose of FPV 1400 mg BID.
c. Up to a maximum dose of FPV/RTV 700/100 mg BID.

In the current supplement, the Applicant is seeking to extend the indication for a BID regimen of FPV/RTV to HIV-infected infants and children 4 weeks to <6 years of age using the currently marketed FPV oral suspension formulation administered concurrently with RTV oral solution. Data from two trials and an integrated population PK analysis (see Pharmacometrics review, Appendix) were submitted to the supplemental NDA (sNDA) to support the dosing and claims proposed in this submission. The first trial (APV29005) evaluated the PK, safety, and antiviral activity of a twice-daily regimen of RTV-boosted FPV in treatment-naïve and -experienced pediatric subjects 2 to <6 years of age. The second trial (APV20002) evaluated the PK, safety, and antiviral activity of a twice-daily regimen of RTV-boosted FPV in treatment-naïve and -experienced pediatric subjects 4 weeks to <2 years of age. For both trials, the primary objective was to identify a FPV/RTV dosage regimen(s) which provides similar steady-state amprenavir exposures to those demonstrated to be safe and effective in adults, with specific focus on the adult FPV/RTV 700/100 mg BID regimen. Data from a third trial (APV20003) which evaluated the PK, safety, and antiviral activity of a once-daily regimen of FPV/RTV in pediatric subjects 2 to <18 years of age submitted in this sNDA provides supportive safety data for this submission.

(b) (4) During the review cycle, the Division requested that the Applicant submit dosing recommendations based on weight bands because it was postulated that weight-based dosing could provide more consistent amprenavir exposures across the 4 weeks to <6 years old population and allow for a more simplified dosing scheme (**Table 4**). In addition, the Applicant was asked to provide simulations that compared exposures for pediatrics using the (b) (4) dosing recommendations based on weight bands and age bands to exposures in adults. The simulations demonstrated that plasma APV exposures in subjects 4 weeks to <6 years of age are similar when using either weight- or age-band dosing (see Pharmacometric Review, Appendix).

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the data submitted in NDA 21548 S-028 and NDA 22116 S-012 and agree that from a clinical pharmacology perspective it supports the proposal to introduce a dosing regimen of twice daily FPV/RTV for HIV-infected infants and children 4 weeks to <6 years of age. We concur with the Applicant's proposed weight band-based dosing recommendations; however, we propose that for infants 4 weeks to <6 months of age the indication be restricted to treatment-naïve patients only given that only treatment-naïve subjects were studied in this age group and APV exposures achieved using the proposed dosage regimen were similar to exposures achieved in adults receiving FPV/RTV 1400/100 mg QD, a regimen approved for use in treatment-naïve adults only. Edits to the proposed label are recommended (see Section 3, Detailed Labeling Recommendations).

Table 5 shows the updated pediatric dosing information based on the recommendations of the Division.

Table 5 – Twice-Daily Dosage Regimens for PI-Naïve Pediatric Patients 4 Weeks of Age and for PI-Experienced Pediatric Patients 6 Months of Age Using Lexiva Oral Suspension with Concurrent Ritonavir (Based on the Division's Recommendation)

Weight	LEXIVA plus Ritonavir BID
< 11 kg	LEXIVA 45 mg/kg plus ritonavir 7 mg/kg[a]
11 kg - <15 kg	LEXIVA 30 mg/kg plus ritonavir 3 mg/kg[a]
15 kg - <20 kg	LEXIVA 23 mg/kg plus ritonavir 3 mg/kg[a]
≥20 kg	LEXIVA 18 mg/kg plus ritonavir 3 mg/kg[a]

1.2 Phase IV Commitments

None

1.3 Summary of Key Clinical Pharmacology and Biopharmaceutics Findings

Fosamprenavir (FPV), a pro-drug of amprenavir (APV), is a protease inhibitor approved for the treatment of HIV-1 infection in adults and certain portions of the pediatric population. FPV is commercially available as a 700-mg strength tablet and as an oral suspension (50 mg/mL).

FPV can be administered alone ("un-boosted") or can be co-administered with ritonavir (RTV) ("boosted"), another HIV protease inhibitor. Ritonavir (RTV) is a potent inhibitor of the CYP3A4 enzyme which metabolizes APV, and therefore its co-administration with FPV leads to an increase in APV plasma concentrations. Treatment-experienced patients often harbor more resistant virus and require higher trough concentrations. An un-boosted FPV regimen is approved for treatment-naïve patients, while boosted FPV regimens are approved for treatment-naïve and -experienced patients (in both adults and pediatrics).

In this supplement, the Applicant is seeking to introduce a FPV/RTV BID dosing regimen for treatment-naïve and -experienced infants and children 4 weeks to less than 6 years of age. This review summarizes the clinical pharmacology results from two pivotal clinical trials (APV29005 and APV20002) that were submitted to support dosing recommendations for the twice-daily boosted regimen. The applicant has submitted 24-week interim safety and efficacy data.

APV29005

Reviewer Comment:

Trial APV29005 evaluated FPV BID and FPV/RTV BID regimens in pediatric subjects 2 to 18 years old. For the purposes of this submission, the review of the results of this study focus primarily on the PI-naïve or -experienced subjects ages 2 to <6 years old receiving FPV/RTV BID for whom dosing is currently being proposed. Dosing regimens for PI-naïve patients ≥2 years old (FPV BID) and for PI-naïve or -experienced patients ≥6 years old (FPV/RTV BID) evaluated in APV29005 have been reviewed, approved, and labeled by the Agency in a previous review submission (see NDA 22116 Clinical Pharmacology review authored by Dr. Vikram Arya; submission date 12/13/06).

This trial was a 48-week, Phase 2, open-label, non-comparative PK, safety, and antiviral activity trial conducted in treatment-naïve and -experienced pediatric subjects 2 to <6 years of age in

which a twice-daily FPV/RTV regimen was evaluated (in addition, all subjects were on ART background regimens consisting of 2 nucleoside reverse transcriptase inhibitors [NRTIs]). Originally a dose of FTV/RTV 20/4 mg/kg BID was to be evaluated in this study; however based on simulations from a population PK model which predicted this dose would result in exposures that would be too low, the protocol was amended to evaluate a FPV/RTV 23/3 mg/kg BID dosage regimen, which was predicted by the model to provide AUC(0-τ) and Cτ comparable to those observed in adults receiving FPV/RTV 700/100 mg BID. Therefore, all subjects received FPV/RTV 23/3 mg/kg BID. **Table 6** summarizes the steady-state plasma APV PK parameters achieved in 14 subjects 2 to < 6 years old who received FPV/RTV 23/3 mg/kg BID and statistical comparisons to historical adults.

Table 6 – Summary of Steady-State Plasma APV PK Parameters and Statistical Comparisons for FPV/RTV BID in Pediatric Subjects 2 to <6 Years Old and Historical Adults

Plasma APV PK Parameter	2 to <6 Years[a,c] 23/3 mg/kg BID N=14	Historical Adult 700/100 mg BID[a,c,d] N=159	2 to <6 Years vs. Historical Adult[b,d]
AUC(0-τ) (h.µg/mL)	55.3 (37.9, 80.7) [73]	37.0 (35.1, 38.9) [33]	1.50 (1.27, 1.77)
Cmax (µg/mL)	8.66 (6.08, 12.3) [67]	5.62 (5.35, 5.92) [33]	1.54 (1.30, 1.82)
Cτ (µg/mL)	3.59 (2.60, 4.97) [64]	2.17 (2.05, 2.30) [38]	1.66 (1.35, 2.04)
CL/F (mL/min/kg)	6.06 (4.12, 8.91) [75]	3.52 (3.33, 3.71) [35]	1.72 (1.45, 2.05)
CL/F (mL/min)	91.2 (60.0, 139) [83]	270 (257, 284) [33]	0.338 (0.280, 0.407)
tmax (h)	1.25 (1.00, 4.00)	1.50 (0.50, 6.00)	ND
t1/2 (h)	5.21 (4.47, 6.08) [27]	ND	ND

Table 7 shows the major APV PK-related conclusions from Study APV29005.

Table 7 – Major APV PK-Related Conclusions from Study APV29005

Age Range	FPV/RTV Dosage Regimen	PK Conclusions
2 to <6 years	23/3 mg/kg BID	50% higher AUC(0-τ); 54% higher C_{max}; and 66% higher C_τ as compared to values historically observed for adults receiving FPV/RTV 700/100 mg BID

Reviewer Comment:

Amprenavir exposures in pediatric subjects 2 to <6 years of age receiving FPV/RTV 23/3 mg/kg BID were higher than exposures achieved in adults receiving FPV/RTV 700/100 mg BID, yet were contained within the upper limit of the pre-defined PK target for $AUC_{0-\tau}$ by being lower than 61.68 h·µg/mL (based on the 95th percentile observed in adults). While mean AUC and Cmax achieved in the 2 to <6 year old age group was 50 % and 54% higher, respectively, as compared to adults, there was no discernible difference in the safety profile between the two populations.

[redacted] (b) (4)

Reviewer Comment:
Of the 14 subjects in study APV29005 who received FPV/RTV 23/3 mg/kg BID and contributed data to the PK profile summary, there were 3 subjects who were 2 years old. Mean exposures ($AUC_{0-\tau}$ and Cmax) achieved in these three subjects were lower compared to mean exposures in subjects 3 to <6 years of age; however their exposures were similar to that attained in the historical adult population **(Table 8)**. *For both the 2 to <3 and 3 to <6 year old age groups, mean Cτ was higher compared to adults.*

Table 8 – Summary of Steady-State Plasma APV PK Parameters and Statistical Comparisons for FPV/RTV BID in Subjects 2 to <3 Years Old and 3 to <6 Years Old and Historical Adults

Plasma APV PK Parameters	2 to <3 Years[a] 23/3 mg/kg BID N=3	3 to <6 Years[a] 23/3 mg/kg BID N=11	Historical Adult 700/100 mg BID N=159	2 to <3 Years vs. Historical Adult[b]	3 to <6 Years vs. Historical Adult[b]
AUC(0-τ) (h·µg/mL)	41.8	59.7	37.0	1.13	1.61
Cmax (µg/mL)	5.51	9.80	5.62	0.99	1.74
Cτ (µg/mL)	3.70	3.58	2.17	1.71	1.65

a Geometric Mean
b GLS Mean Ratio

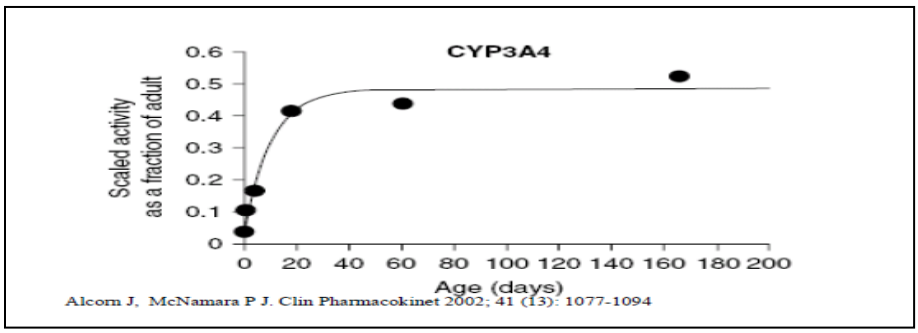
While [redacted] (b) (4) dosing [redacted] (b) (4) for pediatric patients 2 to <3 years of age is not appropriate based solely on age, when looking at the pharmacokinetic data across the two studies (APV20002 and APV29005), it is apparent that a higher mg/kg dose (FPV/RTV 30/3 mg/kg BID) would be appropriate for subjects within a particular weight-band which could extend the age group to include subjects greater than 18 months. This prompted the Division to request that the Applicant submit a proposal for dosing recommendations based on weight-bands [redacted] (b) (4). In addition, the Applicant was asked to provide simulations that compared exposures for pediatrics using the [redacted] (b) (4) dosing recommendations based on weight bands and age bands to exposures in adults (see Pharmacometric Review, Appendix).

APV20002
This trial was a 48-week, Phase 2, open-label, non-comparative, PK, safety and antiviral activity trial conducted in 54 treatment-naïve and -experienced infants and children 4 weeks to <2 years

of age in which a twice-daily FPV/RTV regimen was evaluated (in addition, all subjects were also on ART background regimens consisting of 2 NRTIs) . Subjects were divided into two cohorts based on age: 4 weeks to <6 months (N=26) and 6 months to <2 years (N=28). All subjects in the 4 weeks to <6 months age cohort happened to be protease inhibitor (PI)-naïve. For the 6 months to <2 years age cohort, 23 were PI-naïve and 5 were PI-experienced.

The youngest subject enrolled in study APV20002 was 9 weeks of age. The Applicant is proposing the extrapolation of dosing down from pediatric patients 9 weeks of age to infants 4 weeks of age. APV is primarily eliminated by CYP3A4 metabolism in both adults and children. The differences in intrinsic clearance between adults and infants have been attributed to the functional ontogeny of the CYP3A4 enzyme. The Applicant presented *in vitro* data from the scientific literature which indicates CYP3A4 hepatic microsomal activity expressed as a fraction of adult activity and scaled to *in vivo* activity data (solid symbols) appears to plateau after 20 days of life (APPEARS THIS WAY ON ORIGINAL), suggesting that a 1 month old patient would have similar capacity to metabolize APV as a 2 or 3 month old patient.

Figure 1 – CYP3A4 Fraction of Adult Activity by Age



Reviewer Comment:
The extrapolation of dosing to pediatric patients 4 weeks of age is reasonable. Further support for this extrapolation can be provided by pediatric studies with lopinavir. The HIV-1 protease inhibitor lopinavir administered in combination with ritonavir is approved for treatment of HIV-1 infection in adults and children down to the age of 14 days. Lopinavir is also metabolized primarily by CYP3A4. Based on pharmacokinetic data from the clinical trial which evaluated lopinavir/ritonavir in infants less than 6 months of age, lopinavir clearance in this age group was higher compared to older children and adults, but was similar in the 14 day to <6 month age group. Therefore the same mg/kg dose was approved for use across the 14 day to <6 month population.

Single-dose and multiple-dose PK was evaluated in an initial subset of enrolled subjects in order to inform the selection of a chronic regimen for study. Based on the initial PK data the following chronic regimens were evaluated in the 4 weeks to <6 months cohort: FPV/RTV 45/10 mg/kg BID and 60/10 mg/kg BID. The following regimens were evaluated in the 6 months to <2 years cohort: FPV/RTV 45/7 mg/kg BID and 60/10 mg/kg BID. **Table 9** and Error! Reference source not found. summarize the steady-state APV PK parameters achieved in the 4 weeks to <6 months age cohort and the 6 months to <2 years age cohort, respectively, and their comparisons to historical adult data.
APV clearance was similar across the 4 weeks to <2 year old age range.

Table 9 – Summary of Steady-State Plasma APV PK Parameters and Statistical Comparisons for FPV/RTV BID in Pediatric Subjects in the 4 weeks to <6 Months Age Group and Historical Adults

Plasma APV PK Parameter	4 Weeks to <6 Months[a]		Historical Adult 700/100 mg BID[a,c,d] N=79	4 Weeks to <6 months vs. Historical Adults[b,d]	
	45/10 mg/kg BID N=9[c]	60/10 mg/kg BID N=3[c]		45/10 mg/kg BID	60/10 mg/kg BID
AUC(0-τ) (h·µg/mL)	26.6 (15.2, 46.8) [84]	47.2 (19.9, 112) [36]	37.0 (35.1, 38.9) [33]	0.720 (0.542, 0.957)	1.28 (0.786, 2.08)
Cmax (µg/mL)	6.25 (3.82, 10.2) [71]	10.8 (7.25, 16.2) [16]	5.62 (5.35, 5.92) [33]	1.11 (0.853, 1.45)	1.93 (1.22, 3.04)
Cτ (µg/mL)	0.860 (0.500, 1.48) [96]	1.99 (0.892, 4.44) [54]	2.17 (2.05, 2.30) [38]	0.397 (0.305, 0.516)	0.918 (0.619, 1.36)

a. Geometric Mean (95% CI) [CVb%]
b. GLS Mean Ratio (90% CI)
c. N=16 for 45/10 mg/kg BID Cτ, N=4 for 60/10 mg/kg BID Cτ, N=158 for historical adult AUC(0-τ)
d. Healthy Adults

Table 10 – Summary of Steady-State Plasma APV PK Parameters and Statistical Comparisons for FPV/RTV BID in Pediatric Subjects in the 6 Months to <2 Years Age Group and Historical Adults

Plasma APV PK Parameter	6 Months to <2 Years[a]		Historical Adult 700/100 mg BID[a,c,d] N=79	6 months to <2 Years vs. Historical Adults[b,d]	
	45/7 mg/kg BID N=10[c]	60/7 mg/kg BID N=9[c]		45/7 mg/kg BID	60/7 mg/kg BID
AUC(0-τ) (h·µg/mL)	27.5 (14.5, 52.1) [110]	48.4 (12.9, 181) [334]	37.0 (35.1, 38.9) [33]	0.744 (0.568, 0.975)	1.31 (0.969, 1.77)
Cmax (µg/mL)	5.84 (3.35, 10.2) [91]	10.4 (3.64, 30.0) [235]	5.62 (5.35, 5.92) [33]	1.04 (0.807, 1.34)	1.86 (1.43, 2.42)
Cτ (µg/mL)	1.99 (1.56, 2.53) [68]	2.76 (1.70, 4.47) [89]	2.17 (2.05, 2.30) [38]	0.917 (0.772, 1.09)	1.27 (0.989, 1.64)

a. Geometric Mean (95% CI) [CVb%]
b. GLS Mean Ratio (90% CI)
c. N=28 for 45/7 mg/kg BID Cτ, N=12 for 60/7 mg/kg BID Cτ, N=158 for historical adult AUC(0-τ)
d. Healthy Adults

Table 11 summarizes the major PK related conclusions for study APV20002

Table 11 – Major PK-related Conclusions from Study APV20002

Age Range	FPV/RTV Dosing Regimen	PK Conclusions
4 weeks to <6 months	45/10 mg/kg BID	28% lower $AUC_{0-\tau}$, 11% higher C_{max}, and 60% lower C_τ as compared to values historically observed for healthy adults receiving FPV/RTV 700/100 mg BID
4 weeks to <6 months	60/10 mg/kg BID	28% higher $AUC_{0-\tau}$, 93% higher C_{max}, and 8% lower C_τ as compared to values historically observed for adults receiving FPV/RTV 700/100 mg BID
6 months to <2 years	45/7 mg/kg BID	26% lower $AUC_{0-\tau}$, 4% higher C_{max}, and 8% lower C_τ as compared to values historically observed for adults receiving FPV/RTV 700/100 mg BID
6 months to <2 years	60/7 mg/kg BID	31% higher $AUC_{0-\tau}$, 86% higher C_{max}, and 27% higher C_τ as compared to values historically observed for adults receiving FPV/RTV 700/100 mg BID

Based on the data from Study APV20002, the [redacted] (b) (4) dosage regimen [redacted] (b) (4) of FPV/RTV 45/7 mg/kg BID for pediatric patients 4 weeks to <2 years of age.

As shown in Error! Reference source not found., mean exposures attained in subjects 6 months to <2 years of age receiving FPV/RTV 45/7 mg/kg BID were to similar to those observed in adults receiving FPV/RTV 700/100 mg BID. The higher dose of FPV/RTV 60/10 mg/kg BID in pediatrics less than 6 months of age and 60/7 mg/kg BID in pediatrics greater than 6 months of age resulted in a Cmax that was 93% and 86% higher respectively, as compared to adults.

For subjects in the 4 weeks to <6 months age cohort, the majority received a regimen of FPV/RTV 45/10 mg/kg BID (N=9); however, 2 subjects received individualized regimens of FPV/RTV 45/7 mg/kg BID and contributed to the PK profile of that regimen. These two subjects had slightly higher APV exposure than the FPV/RTV 45/10 mg/kg BID group with geometric mean APV AUC(0-τ) of 35.1 h·µg/mL (n=2), Cmax of 8.20 µg/mL (n=2), and Cτ 1.76 µg/mL. The RTV 10 mg/kg BID dose resulted in plasma RTV exposures that were considerably higher than adult ritonavir exposures yet provided no additional increase in plasma APV exposure over the RTV 7 mg/kg BID dose in pediatric subjects receiving FPV 45 mg/kg BID dosing. [redacted] (b) (4)

Reviewer Comment:
Compared to exposures achieved in adults receiving FPV/RTV 700/100 mg BID, subjects 4 weeks to less than 6 months, all of whom were PI-naïve, receiving FPV/RTV 45/10 mg/kg BID attained mean Cτ that were 60% lower. Despite this, virologic response (assessed as proportion of subjects achieving HIV RNA levels <400 copies/mL at week 24) in the 4 weeks to <6 months age cohort was 73%, which was similar to the response observed in adults (58%) and other pediatric age groups receiving FPV/RTV BID: 71% for the 6 months to <2 years age group; 84% for the 2 to <6 years age group; and 53% and 63% for the 6 to <12 years and 12 to <18 years age groups, respectively. There were 7 subjects in study APV20002 who were classified as virologic failures, of whom 2 (Subject 8659 and Subject 8663) were in the 4 weeks to <6 months age cohort and received the FPV/RTV 45/10 mg/kg BID dosage regimen. Based on the virology analysis it was concluded that virologic failure in these subjects was not due to amprenavir-resistance associated substitutions (see Microbiology Review authored by Dr. Lalji Mishra).

Low Cτ in patients taking antiretroviral agents is of critical concern because it can lead to the development of viral resistance. Infants in particular tend to have greater viral loads compared to older populations and the high level of viral replication creates increased potential for mutations. Subtherapeutic drug concentrations in this population could lead to the development of viral resistance and limit future treatment options. If one were to scale the FPV dose in the 9 subjects who received FPV/RTV 45/10 mg/kg BID to 60/7 mg/kg BID (by multiplying the mean APV PK parameter values by 1.33) in an attempt to achieve higher exposures in the 4 weeks to <6 months age group, it would result in an AUC that was closer to that observed in adults receiving FPV/RTV 700/100 mg BID. (The PK for APV are linear in this exposure range and can thus be scaled in this fashion.) However, this increase in dose would result in a higher Cmax than adults and only a marginal increase in Cτ (**Table 12***).*

Table 12 – Predicted APV PK Parameters in Pediatrics 4 weeks to <6 months for a Dose of FPV/RTV 60/7 mg/kg BID and Statistical Comparison to Historical Adults

Plasma APV PK Parameter	Pediatric exposure if dose was scaled to 60/7 mg/kg BID (n=9)	Ratio to adult (700/100 mg BID)
AUC_{12} (h·µg/mL)	35.5	0.96 (0.72, 1.28)
C_{max} (µg/mL)	8.4	1.48 (1.13, 1.93)
Cτ (µg/mL)	1.1	0.53 (0.41, 0.69)

It should also be noted that if a higher dose of FTV/RTV 60/7 mg/kg BID were to be proposed for this age group, it would require larger FPV suspension volumes for subjects weighing less than 9 kg.(**Table 13**).

Table 13 – FPV Solution Volume Requirements by Dose for Pediatric Patients Weighing 3 to 22 kg

Pediatric Body Weight (kg)	Weight-band dosing	Volume (mL)	Increased FPV dose in pediatrics <9 kg	Volume (mL)
3	45 mg/kg	2.7	60 mg/kg	3.6
6		5.4		7.2
8		7.2		9.6
9		8.1	45 mg/kg	8.1
11		9.9		9.9
12	30 mg/kg	7.2	30 mg/kg	7.2
14		8.4		8.4
15	23 mg/kg	6.9	23 mg/kg	6.9
19		8.7		8.7
20	18 mg/kg	7.2	18 mg/kg	7.2
22		7.9		7.9

A total of 26 subjects were included in the 4 weeks to <6 months population in Study APV20002. All 26 subjects were PI-naïve. When comparing the mean exposures (AUC_{24}, Cmax, and Cτ) attained in the group receiving FPV/RTV 45/10 mg/kg BID to exposures attained

from the various approved FPV/RTV regimens in adults, it was observed that all three PK parameters were most comparable to parameters observed in adults receiving the FPV/RTV 1400/100 mg QD regimen (**Table 14**).

Table 14 – Observed APV Plasma PK Parameters from Pediatrics 4 weeks to <6 months receiving FPV/RTV 45/10 mg/kg BID and the Statistical Comparisons to Approved Adult FPV/RTV Dosage Regimens

Plasma APV PK Parameter	45/10 mg/kg BID (n=9)	Ratio to adult (700/100 mg BID)	Ratio to adult (1400/200 mg QD)	Ratio to adult (1400/100 mg QD)
AUC_{24} (h·µg/mL)	53.2	0.72	0.77	0.80
C_{max} (µg/mL)	6.3	1.11	0.88	0.80
C_T (µg/mL)	0.86	0.40	0.59	1.00

Reviewer Comment:
The PK matching assessment demonstrated that the exposures achieved in pediatric subjects 4 weeks to <6 months of age receiving FPV/RTV 45/10 mg/kg BID were lower than exposures achieved in adults receiving FPV/RTV 700/100 mg BID, but best matched exposures achieved in adults receiving a regimen of FPV/RTV 1400/100 mg QD. This regimen is approved for treatment-naïve adults only. Based on this, it is recommended that the indication for the treatment of HIV-1 infection in pediatrics less than 6 months of age be restricted to those patients who are PI-naïve.

2 QUESTION-BASED REVIEW

2.1 General Attributes

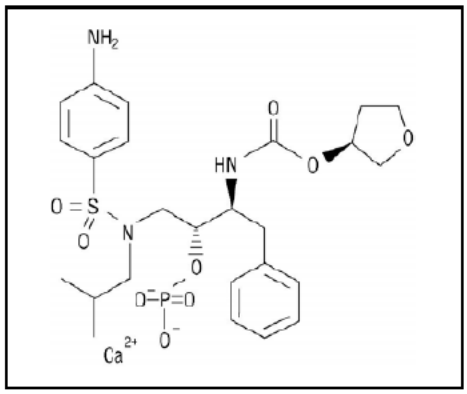
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Fosamprenavir calcium (Lexiva, FPV) is the phosphate ester prodrug of the HIV-protease inhibitor amprenavir (APV). FPV is currently commercially available as a tablet formulation (700 mg strength) and an oral suspension (50 mg/mL). FPV is rapidly and extensively converted to amprenavir ($C_{25}H_{35}N_3O_6S$; 505.64) by alkaline phosphatases at the apical endothelium of the intestinal membrane.

Chemical name: (3*S*)-tetrahydrofuran-3-yl (1*S*,2*R*)-3-[[(4-aminophenyl) sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt

Structure:

Figure 2 – Structure of Fosamprenavir Calcium



Molecular formula: $C_{25}H_{34}CaN_3O_9PS$
Molecular weight: 623.7
Formulation: oral suspension, tablet
Composition: oral suspension – is a white to off-white suspension which has a bubblegum odor. The product contains 50 mg/mL of fosamprenavir as the calcium salt, equivalent to approximately 43 mg of amprenavir. It is packaged into 8 oz. white, round high density polyethylene bottles with (b) (4) closures at a fill-volume of 225 mL.

Table 15 lists the composition of Lexiva oral suspension:

Table 15 – Composition of Lexiva Oral Suspension

Component	Quantity (mg/mL)	Function	Reference to Standard
Fosamprenavir calcium	61.0[1]	Active	(b) (4)
Propylene glycol	(b) (4)	(b) (4)	USP
Hypromellose (b) (4)			NF
Sucralose			NF
Methylparaben			NF
Propylparaben			NF
Polysorbate 80			NF
Calcium chloride dihydrate			USP
Artificial Grape Bubblegum flavor (b) (4)			Supplier
Natural Peppermint flavor (b) (4)			Supplier
Purified water			USP
Total unit dose	1.0 mL	--	-

Note:
1. Equivalent to 50 mg of fosamprenavir. (b) (4) (b) (4)

Composition: tablet – is a white to cream colored solid with a solubility of approximately 0.31 mg/mL in water at 25˚C. The product contains 700 mg of fosamprenavir as the calcium salt, equivalent to approximately 600 mg of amprenavir.

Reviewer Comment:
Lexiva oral suspension contains propylene glycol [redacted] *The amount of propylene glycol contained in Lexiva oral suspension is considerably lower than that contained in Kaletra oral solution* [redacted] *an ARV that has associated toxicity in preterm neonates secondary to adverse events related to large amounts of propylene glycol. Although the amount of propylene glycol in Lexiva oral suspension is small, it is important that the total amount of propylene glycol from all medicines that are to be given, particularly to pediatric patients less than 6 months of age, be taken into account in order to avoid potential toxicity (i.e., hyperosmolality, CNS depression, and seizures) associated with this excipient.*

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Fosamprenavir is a prodrug of amprenavir, an inhibitor of human immunodeficiency virus (HIV) protease. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles. Fosamprenavir is indicated in combination with other antiretroviral drugs for the treatment of HIV-1 infection.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

[redacted]

During the review cycle, the Division requested that the Applicant propose dosage regimens based on weight bands. The Applicant's proposed weight-band based dosage regimens are shown in the table below:

Patient Population	Weight	Lexiva/Ritonavir Dosage Regimen
Treatment-naïve or treatment-experienced	[redacted]	45/7 mg/kg BID
		30/3 mg/kg BID[b]
		23/3 mg/kg BID
		18/3 mg/kg BID

b Dose has not been evaluated during the clinical trial and is proposed based on modeling and simulation

Following review of the data included in the two pivotal Phase 2 trials and the integrated population PK model, the Division is in agreement that weight-band based dosing should be recommended and is proposing the following twice daily FPV/RTV dosage regimens for PI-naïve pediatric patients 4 weeks of age or greater and for PI-experienced pediatric patients 6 months of age or greater using Lexiva oral suspension:

Weight	LEXIVA plus Ritonavir BID
< 11 kg	LEXIVA 45 mg/kg plus ritonavir 7 mg/kg[a]
11 kg - <15 kg	LEXIVA 30 mg/kg plus ritonavir 3 mg/kg[a]
15 kg - <20 kg	LEXIVA 23 mg/kg plus ritonavir 3 mg/kg[a]
≥20 kg	LEXIVA 18 mg/kg plus ritonavir 3 mg/kg[a]

Pediatric patients should take FPV oral suspension with food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The following studies were used to support dosing or dosing claims:

Study APV20002 is an international, 48-week, open-label, 2-cohort, multicenter trial conducted in HIV-1 infected, treatment-naive and -experienced pediatric subjects ages 4 weeks to less than 2 years old. The primary objective of this study was to determine FPV/RTV dosing regimen(s) which achieved steady-state APV exposures similar to that observed in adults and demonstrate acceptable safety and anti-viral activity. Single-dose PK was evaluated in an initial subset of subjects to inform the selection of a FPV/RTV dosage regimen for repeated administration to be evaluated in the trial. All subjects receiving FPV/RTV twice daily (n=31 contributed to the PK population) underwent intensive PK sampling at either Week 2 or Week 8 (at the following time points: 0 hours (predose) and at 1, 2, 4, 6, 8 and 12 hours post-dose) and additional PK trough sampling at Weeks 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Study APV29005 is an international, 48-week, Phase 2, open-label, non-comparative, multi-cohort, multicenter study conducted in HIV-1 infected, treatment-naïve and -experienced pediatric subjects 2 to less than 18 years of age. The primary objective of this study was to determine a FPV/RTV BID dosage regimen(s) which achieved steady-state APV exposures similar to that observed in adults and demonstrate acceptable safety and anti-viral activity. All subjects were to (n=14 contributed data for the amprenavir PK profile) undergo intensive PK sampling at the Week 2 visit (at the following time points: 0 hours (predose) and at 1, 2, 4, 6, 8 and 12 hours post-dose) and additional PK trough sampling at Weeks 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary objective of studies of antiretroviral agents in pediatric subjects is to determine dosage regimens that achieve similar steady-state systemic exposures to those found to be safe and effective in the adult population. Thus the primary endpoints in these studies are

pharmacokinetic endpoints. In addition, safety and tolerability of the proposed dosage regimens are assessed.

Since the course of HIV disease is similar between adults and children and the response to protease inhibitor therapy is not expected to be different between the two populations, the efficacy of FPV/RTV therapy observed in adults can be extrapolated to children. Viral load (which when increased is correlated with morbidity and mortality) and CD4+ count (which is an indication of immune status) are accepted surrogate markers for efficacy of antiretroviral agents and are often evaluated as secondary (supportive) endpoints in pediatric trials.

2.2.3 Are the active and or relevant moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure response relationships?

Yes, the appropriate moieties (FPV, APV, and RTV plasma concentrations) were quantified in all of the clinical pharmacology studies. Although no formal exposure-response analysis was performed, plasma APV concentrations were used in the modeling and simulation of proposed dosage regimens.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

In the adult clinical development program, a wide range of fosamprenavir doses were not evaluated due to existing data from the previously marketed Agenerase (AGN, amprenavir) product. The relationships between plasma APV PK parameters and antiviral activity assessment over 4 weeks of dosing in antiretroviral-naive adult subjects were established for AGN in the dose range of 300 mg to 1200 mg BID with 1200 mg BID being selected as the optimal regimen. Fosamprenavir (FPV) doses similar to or higher than AGN 1200 mg BID were selected for evaluation in a Phase 2, multiple-dose study in HIV-infected, treatment-naïve adults (APV20001). Two FPV regimens were evaluated in comparison to the control AGN 1200 mg BID regimen in that trial: FPV 1395 (1200 mg APV molar equivalents) BID and FPV 1860 mg (1600 mg APV molar equivalents). All three regimens achieved similar reductions in plasma HIV-1 RNA levels after 4 weeks of dosing. Short-term safety was also similar between the three regimens. The higher FPV dosage regimen (1860 mg BID) provided similar plasma APV exposures to FPV 1395 mg BID, and therefore did not provide any additional benefit. Based on this data, FPV 1400 mg BID was selected for evaluation in the pivotal phase 3 adult trial (APV30001).

Doses for two FPV regimens that involve co-administration with ritonavir (RTV) were selected for study in adults based on equimolar APV content to approved AGN doses: FPV/RTV 1400/200 mg QD (1200 mg APV molar equivalents) and FPV/RTV 700/100 mg BID (600 mg APV molar equivalents).

In this pediatric supplement, because efficacy of ARVs in the pediatric population can be extrapolated from adults, virologic and immunologic measurements were included as secondary endpoints (i.e., % response rates in comparison to historical adult populations).

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

An exposure-response relationship for safety has not been identified for amprenavir in adults.

In this pediatric submission, safety was not assessed using an exposure-safety relationship, but instead relied on evaluating top-line results (i.e., % adverse events rates in comparison to historical adult populations).

2.2.4.3 Are the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

At this time, the data are insufficient to recommend twice-daily dosing of FPV in combination with ritonavir for PI-experienced pediatric patients less than 6 months of age.

2.2.5 What are the PK characteristics of amprenavir?

The absolute oral availability of amprenavir after administration of Lexiva in humans has not been established. Time to peak amprenavir concentration (T_{max}) occurs between 1.5-4 hours. The administration of a single dose of Lexiva oral suspension in the fasted state provides similar amprenavir exposures ($AUC_{0-\infty}$) but a 14.5% higher C_{max} as compared to single dose administration of Lexiva tablet. Administration of single-dose Lexiva tablets in the fed state compared with the fasted state is associated with no significant changes in amprenavir C_{max}, T_{max}, or $AUC_{0-\infty}$. Therefore, FPV tablets can be administered without regard to food in adults and pediatric patients. Administration of single-dose Lexiva oral suspension in the fed state results in a 46% reduction of C_{max}, 28% reduction in $AUC_{0-\infty}$, and a 0.72-hour delay in T_{max} of amprenavir as compared to administration in the fasted state. FPV oral suspension should be taken with food in pediatric patients in order to improve tolerability and enhance adherence, while adults should take the suspension without food in order to best match amprenavir exposures that would be achieved from FPV tablets.

After oral administration, FPV is rapidly and almost completely hydrolyzed to amprenavir (APV) and inorganic phosphate by phosphatases in the gut epithelium prior to reaching the systemic circulation. APV is highly metabolized in the liver by CYP3A4, with unchanged APV in urine accounting for approximately 1% of the administered dose. Excretion of unchanged APV in feces is minimal.

The steady-state PK of amprenavir after administration of Lexiva, with or without ritonavir, is similar between healthy adult volunteers and HIV-infected individuals. **Table 16** below (extracted from the FPV package insert) summarizes the PK parameters of amprenavir after administration of various FPV regimens to HIV-infected adults. These parameters serve as references for the proposed regimens in pediatric patients.
Table 17 and **Table 18** summarize the PK parameters of amprenavir after administration of various FPV regimens in children and adolescents.

Table 16 – Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters in HIV-infected Adults

Regimen	C_{max} (mcg/mL)	T_{max} (hours)[a]	AUC_{24} (mcg•hr/mL)	C_{min} (mcg/mL)
LEXIVA 1,400 mg b.i.d.	4.82 (4.06-5.72)	1.3 (0.8-4.0)	33.0 (27.6-39.2)	0.35 (0.27-0.46)
LEXIVA 1,400 mg q.d. plus Ritonavir 200 mg q.d.	7.24 (6.32-8.28)	2.1 (0.8-5.0)	69.4 (59.7-80.8)	1.45 (1.16-1.81)
LEXIVA 1,400 mg q.d. plus Ritonavir 100 mg q.d.	7.93 (7.25-8.68)	1.5 (0.75-5.0)	66.4 (61.1-72.1)	0.86 (0.74-1.01)
LEXIVA 700 mg b.i.d. plus Ritonavir 100 mg b.i.d.	6.08 (5.38-6.86)	1.5 (0.75-5.0)	79.2 (69.0-90.6)	2.12 (1.77-2.54)

[a]Data shown are median (range).

Table 17 – Geometric Mean (95% CI) Steady-State Plasma Amprenavir PK Parameters in HIV-infected Children Receiving FPV BID

Parameter	2 to 5 Years	
	n	LEXIVA 30 mg/kg b.i.d.
$AUC_{(24)}$ (mcg•hr/mL)	8	31.4 (13.7, 72.4)
C_{max} (mcg/mL)	8	5.00 (1.95, 12.8)
C_{min} (mcg/mL)	17	0.454 (0.342, 0.604)

Table 18 – Geometric Mean (95% CI) Steady-State Plasma Amprenavir PK Parameters in HIV-infected Children and Adolescent Patients Receiving FPV/RTV BID

Parameter	6 to 11 Years		12 to 18 Years	
	n	LEXIVA 18 mg/kg plus Ritonavir 3 mg/kg b.i.d.	n	LEXIVA 700 mg plus Ritonavir 100 mg b.i.d.
$AUC_{(0-24)}$ (mcg•hr/mL)	9	93.4 (67.8, 129)	8	58.8 (38.8, 89.0)
C_{max} (mcg/mL)	9	6.07 (4.40, 8.38)	8	4.33 (2.82, 6.65)
C_{min} (mcg/mL)	17	2.69 (2.15, 3.36)	24	1.61 (1.21, 2.15)

2.3 Analytical

2.3.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moieties (APV and RTV) were identified and measured in the plasma by using validated LC/MS/MS methods. Furthermore, fosamprenavir (prodrug) was also measured.

2.3.2 Which metabolites have been selected for analysis and why?

No metabolites were selected for analysis.

2.3.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The analytical methods used measured the total concentrations of fosamprenavir, amprenavir, and ritonavir. It is standard practice to measure total concentrations of protease inhibitors.

2.3.4 What bioanalytical methods are used to assess concentrations?

Plasma samples were analyzed for FPV, APV and RTV by (b) (4) under the direction of (b) (4) using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography with tandem mass spectroscopy (HPLC/MS/MS) analysis. The lower limit of quantification (LLQ) for both APV and RTV was 10 ng/mL using a 100 ul aliquot of human plasma. The upper limit of quantification (ULQ) for both APV and RTV was 10,000 ng/mL. The LLQ and ULQ for FPV are 5 ng/mL and 100 ng/mL, respectively. These analytical methods are acceptable.

The analytical performances for Study APV29005 and APV20002 are summarized in the individual study review (see Section 4, Individual Study Review).

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 INDIVIDUAL STUDY REVIEW

4.1 Individual Study Review

4.1.1 APV29005

Title
"A 48 Week, Phase II, Non-Comparative, Open-Label Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Fosamprenavir/Ritonavir BID when administered to HIV-1 Infected, PI-naïve and Experienced, Pediatric Subjects, 2 to 18 Years Old and Fosamprenavir BID Administered to PI-naïve, Pediatric Subjects 2 to < 6 Years Old"

Information Regarding the Clinical Study Sites
This study was conducted in 30 centers: 10 in the US, 2 in Canada, 1 in Belgium, 9 in Spain, 3 in Russia, 2 in Romania, and 3 in South Africa.

Objectives
The primary objectives of this study were as follows:

- To define the FPV/RTV BID dosage regimen(s) which provided target steady-state plasma amprenavir (APV) exposure to pediatric subjects 2 to 18 years of age.
- To evaluate the safety and tolerability of FPV/RTV BID in combination therapy for 48 weeks in human immunodeficiency virus type 1 (HIV-1) infected, protease inhibitor (PI)-naïve and PI-experienced, pediatric subjects 2 to 18 years of age.
- To define the FPV BID dosage regimen(s) which provided target steady-state plasma APV exposure to pediatric subjects 2 to <6 years of age.
- To evaluate the safety and tolerability of FPV BID in combination therapy for 48 weeks in HIV-1 infected, PI-naive, pediatric subjects 2 to <6 years of age.

The secondary objectives of this study were as follows:

- To assess plasma FPV exposure when administered to HIV-1 infected pediatric subjects 2 to 18 years of age.
- To characterize plasma RTV pharmacokinetic (PK) following administration of FPV/RTV BID to pediatric subjects 2 to 18 years of age.
- To investigate the relationship of plasma APV PK to changes in plasma HIV-1 RNA concentrations (vRNA), CD4+ cell counts and to the occurrence of adverse events (AEs).
- To evaluate the antiviral activity of FPV/RTV BID in combination therapy for 48 weeks in HIV-1 infected, PI-naïve and PI-experienced, pediatric subjects 2 to 18 years of age and of FPV BID in combination therapy in PI-naïve pediatric subjects 2 to <6 years of age.
- To evaluate the immunologic activity of FPV/RTV BID in combination therapy for 48 weeks in HIV-1 infected, PI-naïve and PI-experienced, pediatric subjects 2 to 18 years of age and of FPV BID in combination therapy in PI-naïve pediatric subjects 2 to <6 years of age.
- To assess viral resistance patterns and to compare these patterns with treatment outcome.
- To assess subject adherence to study medications.

Study Design

Study APV29005 is an international, 48-week, Phase 2, open-label, multicohort study conducted in PI-naïve and -experienced pediatric subjects 2 to <18 years of age. Subjects successfully completing 48 weeks of therapy could continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. Subjects were enrolled into cohorts based on age and on prior treatment status. The following table summarizes the cohorts enrolled in this study:

Cohort	Age[a]	Treatment Status	Regimen[b]
1A[c]	2 to <6	PI-naïve	FPV BID
1B[c]	2 to <6	PI-naïve or experienced	FPV/RTV BID
2[c]	6 to 12	PI-naïve or experienced	FPV/RTV BID
3[c]	12 to 18	PI-naïve or experienced	FPV/RTV BID (pill regimen)
4[d]	2 to 18	PI-naïve or experienced	FPV/RTV BID

Reviewer Comment:
For the purposes of this submission, the review of the results of this study will focus primarily on Cohort 1b (PI-naïve or -experienced subjects ages 2 to <6 years old receiving FPV/RTV BID) for which dosing is currently being proposed. Dosing regimens for PI-naïve patients ≥2 years old (FPV BID) and for PI-naïve or -experienced patients ≥6 years old (FPV/RTV BID) evaluated in APV29005 have been reviewed and approved by the Agency during a previous review submission (see NDA 22116 Clinical Pharmacology review authored by Dr. Vikram Arya; submission date 12/13/06).

Key Inclusion Criteria

- Male or female 2 to 18 years of age
- Screening plasma HIV-1 RNA ≥400 copies/mL
- Negative serum pregnancy test and willing to use a pre-specified method of contraception (females of child bearing potential)

Key Exclusion Criteria

- Prior history of having received AGN or FPV for >7 days
- Non-nucleoside reverse transcriptase inhibitor (NNRTI) use within 14 days of study drug administration or anticipated need of concurrent NNRTI therapy during the study
- Pregnant or lactating females
- Grade 3 or 4 transaminase levels higher (serum ALT and/or AST) within 28 days prior to study drug administration and/or clinically relevant hepatitis within the previous 6 months
- Presence of any serious medical condition which might compromise the safety of the subject (e.g. hemoglobinpathy, chronic anemia, history of insulin resistance, diabetes, cardiac dysfunction, hepatitis, or clinically relevant pancreatitis)
- Subjects in the initial acute phase of a CDC Clinical Category C event or infection at Baseline
- Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 28 days of study drug administration
- Treatment with immunomodulating agents or any agent with known anti-HIV activity (e.g., hydroxyurea or foscarnet) within 28 days of study drug administration
- Treatment with any of the following medications within 28 days prior to receiving study medication or the anticipated need during the study:

    - Drugs excluded for safety reasons: amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, simvastatin, terfenadine, and triazolam
    - Drugs excluded because they have the potential to decrease plasma protease inhibitor concentration: carbamazepine, dexamethasone, phenobarbital, primidone, rifampin, and St. John's Wort
- Treatment with other investigations drugs/therapies within 28 days prior to receiving study medication
- Known hypersensitivity to any study medications

Formulation(s) Used
FPV oral suspension (50 mg/mL); RTV oral solution (80mg/mL)

Background antiretroviral therapy (ART) options provided by the Applicant included: abacavir (ABC) oral solution (20 mg/mL); lamivudine (3TC) oral solution (10 mg/mL). Subjects unable to utilize ABC and/or lamivudine (3TC) due to their resistance profile or who at the investigator's discretion would not utilize ABC and/or 3TC, obtained their background NRTIs via prescription. None of the components of the various background ARTs would be anticipated to have a significant PK interaction with amprenavir or RTV.

Dose and Administration
All subjects 2 to <6 years old administered FPV/RTV BID received the fosamprenavir oral suspension and the ritonavir oral solution in this trial. The FPV suspension was to be shaken prior to measuring and doses were to be rounded to the nearest 0.1mL. Doses of the RTV solution were rounded to the nearest 0.01 mL. Both FPV oral suspension and the RTV oral solution were measured and administered via separate dosing syringes due to the two liquid formulations being physically incompatible. The parents/guardians of subjects were instructed to administer FPV suspension with food in this trial. Although administration of FPV oral suspension with food lowers plasma APV exposures, it improves tolerability and enhances adherence through taste-masking. The FPV oral suspension and RTV oral solution were to be administered with food to improve tolerability.

Reviewer Comment:
Although it was instructed in the study protocol to administer the FPV/RTV dose with food, according to the CRF, many doses administered at home and on PK days were not administered with food. This could be contributing to the degree of pharmacokinetic variability seen in this study. The lack of administration of the dose with food appeared to equally distribute across age groups and was not seen more frequently in one age group versus another.

If vomiting occurred within 30 minutes of FPV administration, parents/guardians were instructed to re-administer the dose. Study drug was administered at the site on single-dose visits (SDV) and on serial PK visits. All other doses were administered on an out-patient basis. The dose of the study drugs were adjusted throughout the study as subjects' weight increased. Dose adjustments were to occur when the dose would change by ≥10% from the subject's prior calculated dose.

Rationale for Dose Selection
The primary objective was to identify a dosage regimen which achieved steady-state exposures similar to those achieved in historical adults receiving the FPV/RTV 700/100 mg twice daily

regimen. For pediatric subjects receiving FPV/RTV BID, targets PK parameters were defined as summarized below:

PK Visit	Plasma APV PK Target	Basis for Target
Repeat dose FPV/RTV BID	**Lower**: APV Cτ ≥1.48 µg/mL	25th percentile observed in healthy adults receiving FPV/RTV 700/100 mg BID
	Upper: AUC(0-τ) > 61.68 µg·h/mL APV Cτ > 3.52 µg/mL	95th percentile observed in healthy adults receiving FPV/RTV 700/100 mg BID

Initially, a FPV/RTV dosage regimen of 20/4 mg/kg BID was selected for evaluation in study APV29005 based upon preliminary PK data from study APV20003 in which a once daily dosage regimen of FPV/RTV 30/6 mg/kg was evaluated in pediatric subjects ages 2 to <6 years. This regimen resulted in plasma APV exposures that were approximately 30% lower compared to historical adults receiving a once daily FPV/RTV 1400/200 mg regimen and indicated that a higher FPV dosage regimen would be needed to attain exposures similar to adults. However, in an amendment to the protocol for APV29005 (Amendment#3) the dose to be evaluated was revised to FPV/RTV 23/3 mg/kg BID following a population PK analysis which suggested that the FPV/RTV 20/4 mg/kg dose would result in exposures that were too low, and predicted that FPV/RTV 23/3 mg/kg would deliver plasma APV AUC and Cτ similar to adults. All subsequently enrolled subjects received the revised dose.

Assessments

Pharmacokinetics

Subjects underwent intensive PK sampling at steady-state over 12 hours at the Week 2 visit at the following time points: 0 hours (pre-dose) and at 1, 2, 4, 6, 8 and 12 hours post-dose. The 12-hour post-dose sample was later omitted. In addition, all subjects underwent PK trough sampling at Weeks 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter. For each PK sample, 1 mL of whole blood was collected. Plasma PK samples were analyzed for APV, FPV, and RTV concentrations (where applicable).

In order to ensure the consistency of dosing in the weeks leading up to PK sampling, certain protocol provisions were put in place. To improve the quality of the serial PK samples, it was strongly recommended that the administration of study drugs on the evening prior to the Week 2 visit and on the morning of the Week 2 visit (after the pre-dose PK sample was collected) was directly observed by study personnel. All subjects were provided with a "Subject Dosing Card" as a tool to help them record information regarding the study drug dosages administered prior to plasma PK sampling. Dosing cards were filled out every day for the first two weeks of study and subsequently for the three doses prior to each study visit throughout the study for all subjects. The subjects also recorded whether or not he/she spit up or vomited these three doses, if there was any subsequent redosing of the study drugs and information regarding the FPV oral suspension shaking time. If vomiting or spitting up occurred within 30 minutes of administration, subjects or parents/legal guardians were instructed to re-administer the study medications.

Safety

Hematology, clinical chemistry, serum a1-acid glycoprotein (AAG) concentrations (except Baseline), vital signs, height and boy weight, and the evaluation/documentation of AEs and concomitant medications were performed at all study visits. Hepatitis status was evaluated at Baseline. Fasting lipids, glucose and insulin samples were collected at Baseline, Week 24 and Week 48. To evaluate the development of fat redistribution during the subject's participation in the study, a lipodystrophy CRF tool was completed by the investigator at the Baseline and Week 48 visits.

Efficacy

The following evaluations were performed at the Screening visit**,** Day 1 (prior to the first dose of study drug) and at Weeks 2, 4, 8, 12, 16, 24, 36, and 48, every 12 weeks thereafter and at study withdrawal: quantitative plasma HIV-1 RNA levels, lymphocyte subsets (including total lymphocytes, absolute and percent CD4+ and CD8+ cell counts), HIV-associated conditions; and HIV resistance testing.

Plasma samples, at the investigator's discretion, were collected at the Screening visit for NRTI-experienced subjects to help determine background NRTI regimen. Additional samples were collected at Day 1, Weeks 4, 24, and 48, every 12 weeks thereafter and withdrawal visit until FPV became available locally, and stored for possible HIV genotype/phenotype testing in the future. If resistance was assessed at screening, the following efficacy evaluations were performed at a Pre-Baseline visit: CD4+ and CD8+ cell counts and plasma for quantitative HIV-1 RNA levels.

Statistical Methods

Pharmacokinetics

Plasma PK parameters were estimated using non-compartmental methods. For Week 2, plasma APV and RTV $AUC_{(0-\tau)}$, C_{max}, C_{τ}, T_{max}, C_{avg}, CL/F, λz, and t1/2 were calculated. Statistical comparisons were made for plasma APV and RTV PK parameters between the pediatric subjects enrolled in this study and historical adult subject data. Analysis of variance (ANOVA), using SAS (Version 8.2) Mixed Linear Models procedure, considering the combination of age group and dosage regimen as a fixed effect, was performed on log-transformed plasma APV and RTV PK parameters (except T_{max}) to compare each pediatric age group/dosage regimen to historical adult data. Results from these analyses were exponentiated to obtain a point estimate and 90% confidence interval (CI) estimate of the test (pediatric)-to-reference (historical adult) ratio of geometric least squares (GLS) means. The historical adult population includes those adults who received FPV/RTV 700/100 mg BID in studies APV10010, APV10011, APV10012, APV10013, and APV10022.

It was estimated that a minimum of 12 subjects was as an appropriate number to allow an accurate description of plasma APV PK, safety and tolerability for the FPV/RTV BID regimen in the 2 to <6 year old age group. Sample size considerations were based on the following: in APV PK data from previous FPV suspension studies (APV20003 and APV10016), the highest variability in plasma APV PK parameter values was observed in APV20003 where the inter-subject standard deviation of $\log_e(AUC_{(0-\tau)})$ was 0.56, $\log_e(C_{max})$ was 0.64, and $\log_e(C_{\tau})$ was 0.54.

Safety

Exposure to study medication, measured by the number of weeks on study drug, was summarized. The proportion of subjects reporting adverse events was tabulated. Incidence and

severity of all AEs/serious adverse events (SAEs), treatment related AEs, AEs leading to withdrawal and SAEs were summarized.

Laboratory data, electrocardiogram (ECG) and vital signs (absolute values and change from Baseline) were summarized by visit. In addition, the number and percentage of subjects with laboratory values of clinical concern was summarized. The proportion of subjects experiencing changes from Baseline in their National Cholesterol Education Program (NCEP) and DAIDS lipid categories was summarized.

Efficacy

For antiviral response endpoints using continuous viral load and CD4+ cell count data, the 'observed' analysis was used in which all non-missing data up to a visit was used to calculate the summary data for that particular visit. This method was used for the analysis of changes from Baseline. Missing, Switch or Discontinuation equals Failure (MSD=F) analysis and 'observed' analysis were used for the summary of proportion endpoints using viral load data. The Intent-to Treat (Exposed) (ITT[E]) Population was used in antiviral response analyses while Safety Population was used in safety analysis.

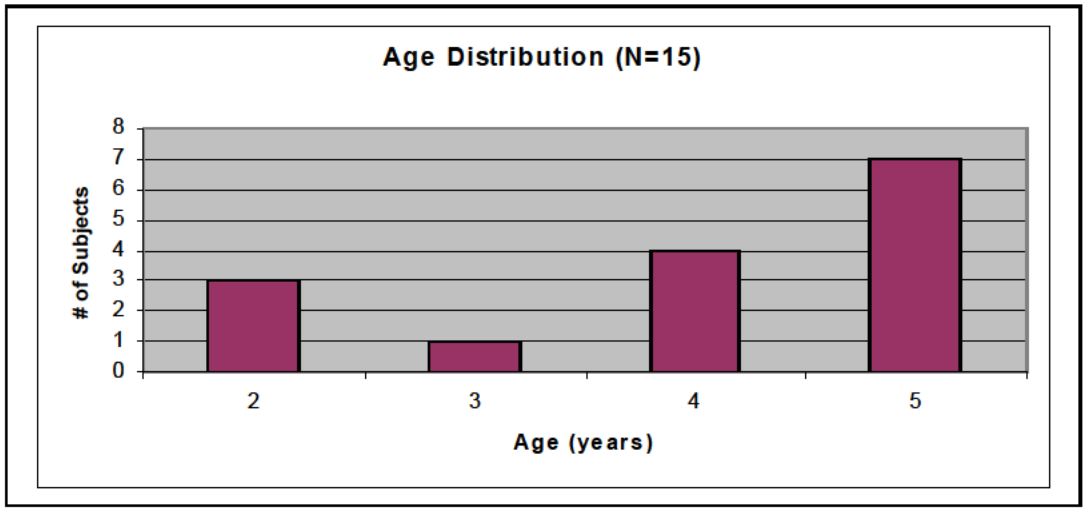
Both ITT(E) and Safety Populations included all subjects with documented evidence of having received at least one dose of investigational treatment.

Results

A total of 89 subjects received repeated FPV/RTV dosing in study APV29005, 19 of whom were between the ages of 2 to <6 years old. Of the 19 subjects included in the exposed population in the 2 to <6 year old age cohort, 6 (32%) were ART and PI-experienced, 6 (32%) were ART-experienced/PI naïve, and 7 (37%) were ART and PI-naïve.

Pharmacokinetics

The PK population (concentration and Cτ) of study APV29005 consisted of 15 subjects 2 to <6 year olds who received the dosage regimen of FPV/RTV 23/3 mg/kg BID. Fourteen of these subjects contributed to the PK profile summary. The table below shows the age distribution for the PK population.



The table below summarizes the steady-state plasma APV PK parameters achieved in pediatric subjects 2 to <6 years old receiving FPV/RTV BID and the statistical comparison to historical adults.

Plasma APV PK Parameter	2 to <6 Years[a,c] 23/3 mg/kg BID N=14	Historical Adult 700/100 mg BID[a,c,d] N=159	2 to <6 Years vs. Historical Adult[b,d]
AUC(0-τ) (h.µg/mL)	55.3 (37.9, 80.7) [73]	37.0 (35.1, 38.9) [33]	1.50 (1.27, 1.77)
Cmax (µg/mL)	8.66 (6.08, 12.3) [67]	5.62 (5.35, 5.92) [33]	1.54 (1.30, 1.82)
Cτ (µg/mL)	3.59 (2.60, 4.97) [64]	2.17 (2.05, 2.30) [38]	1.66 (1.35, 2.04)
CL/F (mL/min/kg)	6.06 (4.12, 8.91) [75]	3.52 (3.33, 3.71) [35]	1.72 (1.45, 2.05)
CL/F (mL/min)	91.2 (60.0, 139) [83]	270 (257, 284) [33]	0.338 (0.280, 0.407)
tmax (h)	1.25 (1.00, 4.00)	1.50 (0.50, 6.00)	ND
t1/2 (h)	5.21 (4.47, 6.08) [27]	ND	ND

Reviewer Comment:
Amprenavir exposures in pediatric subjects 2 to <6 years of age receiving FPV/RTV 23/3 mg/kg BID were higher than exposures achieved in adults receiving FPV/RTV 700/100 mg BID, yet were contained within the upper limit of the pre-defined PK target for $AUC_{0-\tau}$ of >61.68 h·µg/mL (the 95th percentile observed in adults). While mean Cmax and Cτ achieved in the 2 to <6 year old age group was 54% and 66% higher as compared to adults, there was no discernible difference in the safety profile between the two groups.

Based on simulations from the final population PK model, the Applicant proposed a dosing recommendation of FPV/RTV 23/3 mg/kg for pediatric (b) (4) and higher dose of 30/3 mg/kg dose for pediatric patients (b) (4). A FPV/RTV 30/3 mg/kg dose was not studied in the trial.

Reviewer Comment:
Of the 14 subjects in study APV29005 who received FPV/RTV 23/3 mg/kg BID and contributed data to the PK profile summary, there were 3 subjects who were 2 years old. Mean exposures ($AUC_{0-\tau}$ and Cmax) achieved in these three subjects were lower compared to mean exposures in subjects 3 to <6 years of age; however their exposures were similar to that attained in the historical adult population. For both the 2 to <3 and 3 to <6 year old age groups, mean Cτ was higher compared to adults.

The table below summarizes the steady-state plasma APV PK parameters and statistical comparisons for FPV/RTV BID in subjects 2 to <3 years old and 3 to <6 years old and historical adults:

Plasma APV PK Parameters	2 to <3 Years[a] 23/3 mg/kg BID N=3	3 to <6 Years[a] 23/3 mg/kg BID N=11	Historical Adult 700/100 mg BID N=159	2 to <3 Years vs. Historical Adult[b]	3 to <6 Years vs. Historical Adult[b]
AUC(0-τ) (h·µg/mL)	41.8	59.7	37.0	1.13	1.61
Cmax (µg/mL)	5.51	9.80	5.62	0.99	1.74
Cτ (µg/mL)	3.70	3.58	2.17	1.71	1.65

a Geometric Mean
b GLS Mean Ratio

(b) (4)

when looking at the pharmacokinetic data across the two studies (APV20002 and APV29005), it is apparent that a higher mg/kg dose (FPV/RTV 30/3 mg/kg BID) would be appropriate for subjects within a particular weight-band which could extend the age group to include subjects greater than 18 months. This prompted the Division to request that the Applicant submit a proposal for dosing recommendations based on weight-bands (b) (4) *In addition, the Applicant was asked to provide simulations that compared exposures for pediatrics using the proposed dosing recommendations based on weight bands and age bands to exposures in adults (see Pharmacometrics Review, Appendix).*

Bioanalytical

The methods and bioanalysis of FPV, APV, and RTV are acceptable. Concentrations of FPV, APV, and RTV in plasma samples collected during the study were determined using Good Laboratory Practice (GLP) methods and validated liquid chromatography with tandem mass spectroscopy (HPLC/MS/MS) bioanalytical methods. The assays were performed by (b) (4) . All samples were analyzed in the timeframe supported by frozen stability storage data. The long-term stability data for RTV of 600 days and FPV and APV of 836 days (at -20˚C) covers the duration of long-term stability data necessary for Study APV29005.

The lower limit of qualification (LLQ) and upper limit of qualification (ULQ) for FPV were 5 ng/mL and 100 ng/mL and for APV and RTV were 10 ng/mL and 10,000 ng/mL, respectively. Calibration curves were obtained using a linear regression algorithm with 1/concentration weighing of the peak area ration of analyte to internal standard. All coefficients (r) for FPV(GW433908), APV(GW141W94), and RTV(GW278007A) were greater than 0.99. The assay performance for Study APV29005 is shown in the table below:

Assay Performance for Study APV29005 (samples analyzed between 30 September 2004 and 15 December 2011)		
Total Runs		
GW141W94	Accepted Runs 93	Rejected Runs 11
QC Samples	Precision (%CV)* 4.4 to 7.1%	Accuracy (%Dev)* -3.8 to -1.7%
	*Based on QC1, QC2, and QC3 results from accepted runs.	
Calibration Standards	Precision (%CV) 3.3 to 6.4%	Accuracy (%Dev) -2.4 to 1.3%
GW433908	Accepted Runs 87	Rejected Runs 27
QC Samples	Precision (%CV)* 7.1 to 10.5%	Accuracy (%Dev)* -2.0 to -1.4%
	*Based on QC1, QC2, and QC3 results from accepted runs.	
Calibration Standards	Precision (%CV) 5.1 to 6.8%	Accuracy (%Dev)* -0.9 to 1.1%
GW278007A	Accepted Runs 85	Rejected Runs 13
QC Samples	Precision (%CV)* 5.4 to 6.9%	Accuracy (%Dev)* -2.8 to -1.7%
	*Based on QC1, QC2, and QC3 results from accepted runs.	
Calibration Standards	Precision (%CV) 3.9 to 6.7%	Accuracy (%Dev) -1.1 to 1.0%

Inspection Results

The Office of Scientific Investigations was requested to conduct inspections of one of the higher enrolling clinical sites that collected PK data (Center #61333, South Africa) and the bioanalytical laboratory that analyzed the FPV, APV, and RTV plasma samples (b) (4). Following these inspections, it was noted by the inspector that one sample from Subject 000041 at Day 336 (141W94) in study APV29005 was analyzed outside the duration of demonstrated stability and it was subsequently confirmed by the Applicant that the long term storage stability for the sample had been exceeded and therefore, it was concluded by the Inspector that the accuracy of the data from the sample is questionable and should not be accepted for review.

Reviewer Comment:

Subject 00041 was a 5 year old female who was enrolled in study APV29005 and received chronic dosing of FPV 30 mg/kg twice daily without ritonavir; therefore the removal of the data attained from the sample from that subject does not impact the FPV/RTV twice daily PK results from study APV29005 that is currently under review.

No other significant objectionable conditions were observed during the inspections and Form FDA-483 was not issued. The OSI Reviewer concluded that all other PK data from the clinical and bioanalytical portions of the study are acceptable for Agency review (see DSI Consult – Bioequivalence Establishment Inspection Report authored by Dr. Young Moon; dated 03/26/12).

Safety

Thirty-three percent of all subjects in study APV29005 receiving FPV/RTV BID reported at least 1 drug-related treatment-emergent adverse event (AE). Overall, gastrointestinal disorders was the system organ class (SOC) with the highest incidence of drug-related AEs. Vomiting, diarrhea, and nausea were the three most common single drug-related AEs reported. The overall incidence of Grade 3/4 clinical chemistry laboratory abnormalities was 11% in the 87 subjects receiving FPV/RTV BID; 15% of subjects experienced at least one serous adverse event.

Overall the adverse event profile of FPV and FPV/RTV in patients 4 weeks to <2 years old was similar to that of older pediatric patients and adults. However, vomiting with FPV and FPV/RTV regardless of causality did occur in all pediatric age cohorts studied more frequently than in adults.

Efficacy
At Week 24, 16 out of 19 (84%) of subjects 2 to <6 years old receiving FPV/RTV BID achieved RNA levels <400 copies/mL. This proportion of subjects achieving RNA level < 400 copies/mL at Week 24 was greater than that achieved by the 2 to <6 year old (65%), 6 to <12 year old (53%), and 12 to <17 year old (63%) subjects receiving FPV BID alone.

Conclusion
FPV/RTV 23/3 mg/kg BID was generally well tolerated in children 2 to <6 years of age. This regimen in combination with background ARTs provided favorable virologic and immunologic response in this age group, with a safety profile that was similar to that seen in older children and adults. Subjects 2 to <3 years of age achieved APV exposures that were lower than that achieved in subjects 3 to <6 years of age, but were similar to exposures achieved in adults receiving FPV/RTV 700/100 mg. Furthermore, weight-normalized APV clearance was similar in subjects 2 to <6 years of age. Pharmacokinetic modeling predicted FPV/RTV 30/3 mg/kg BID would provide exposures in children 2 to <3 years of age that were comparable to adult exposures.

4.1.2 APV20002

Title
"A 48 Week Phase II, Open-label, 2-cohort, Multicenter Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of FPV (GW433908) and FPV (GW433908)/RTV When Administered to HIV-1 Infected Protease Inhibitor (PI) Naïve and PI-Experienced Pediatric Subjects aged 4 weeks to <2 years"

Information Regarding the Clinical Study Sites
This study was conduced in seven centers: three in South Africa, two in Mexico and one each in Argentina and Portugal.

Objectives
The primary objectives of this study were as follows:

- To define the fosamprenavir/ritonavir BID dosage regimens which will provide target steady-state plasma amprenavir exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years.
- To evaluate the safety and tolerability of FPV/RTV when administered as a component of combination therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years.

The secondary objectives of this study were as follows:

- To evaluate the antiviral activity of FPV/RTV in combination with nucleoside reverse transcriptase inhibitor (NRTI) therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years.
- To evaluate the immunologic activity of FPV/RTV in combination with NRTI therapy in HIV-1 infected pediatric subjects aged 4 weeks to <2 years.

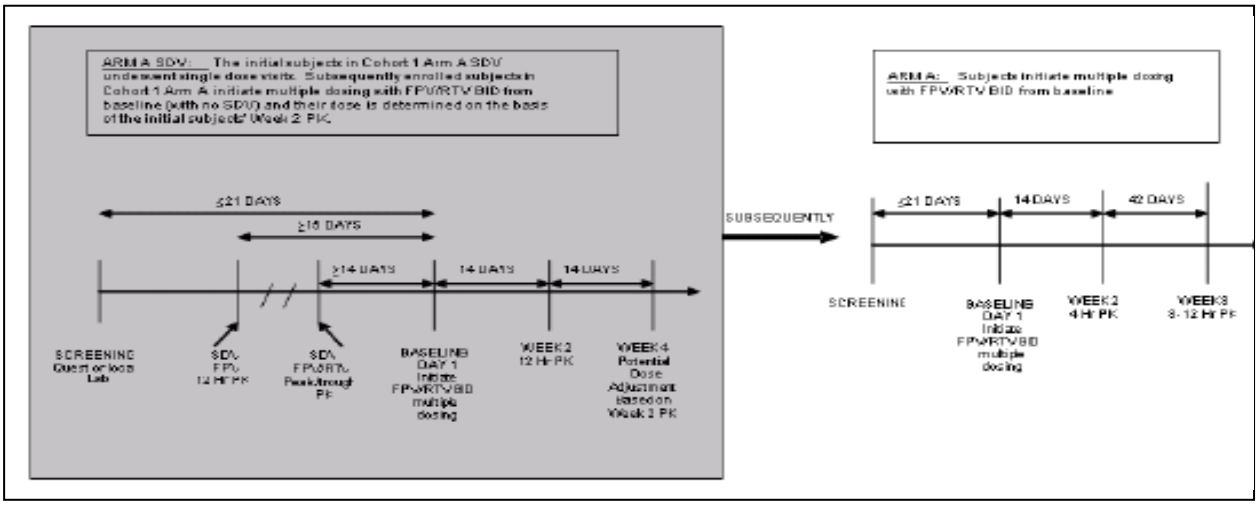
- To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years.
- To assess plasma RTV area under the concentration-time curve over the dosing interval at steady state (AUCτ,ss), maximum plasma concentration at steady state(Cmax,ss) and concentration at the end of a dosing interval at steady state (Cτ,ss) following multiple dose administration of FPV/RTV BID.
- To investigate the relationship of steady-state plasma APV pharmacokinetic (PK) parameters to changes in plasma HIV-1 RNA concentrations, CD4+ percentages and/or the occurrence of adverse events.
- To assess subject adherence and parent/guardian perceptions of study medications.
- To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes).

Study Design

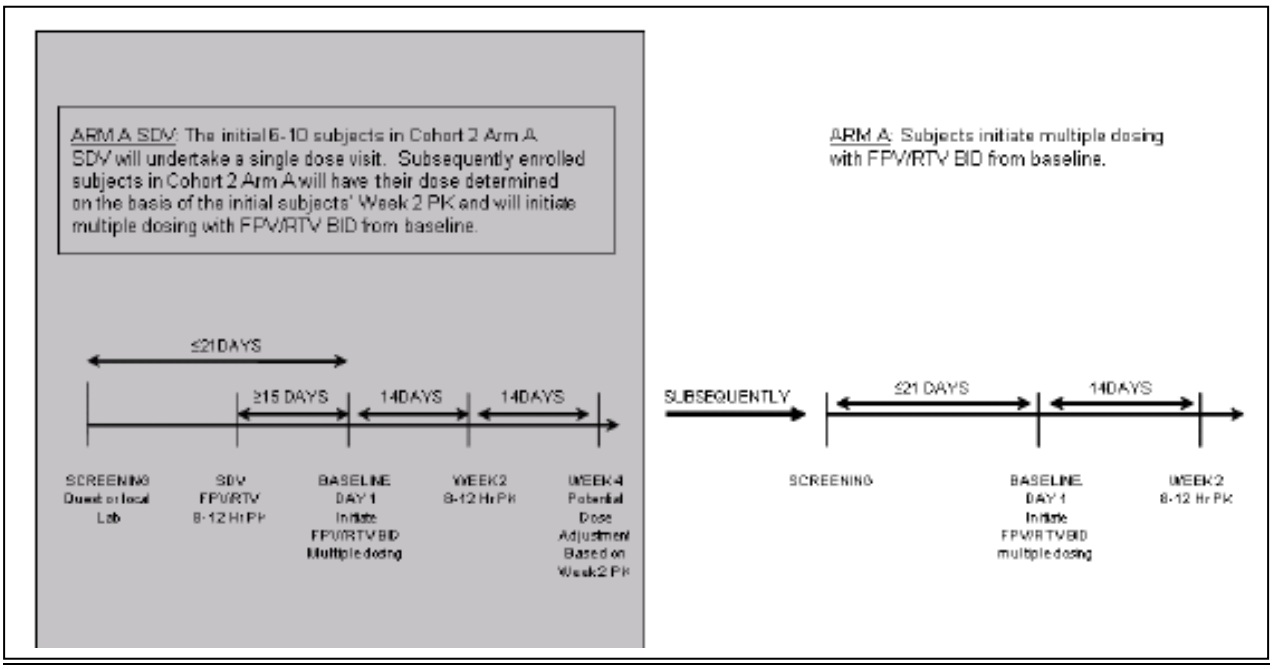
APV20002 is a 48 week, Phase 2, open label, 2-cohort, multicenter study conducted in 59 HIV-1 infected subjects 4 weeks to <2 years old. Subjects successfully completing 48 weeks of therapy could continue in the study with visits every 12 weeks until commercial supplies of FPV oral suspension are available locally and pediatric dosing is approved in the relevant age groups. Subjects were divided into two cohorts based on age: Cohort 1A included 28 subjects age 6 months - <2 years and Cohort 2A included 26 subjects age 4 weeks- <6 months. A sample size of 24 subjects was originally planned for this study; however, this number was exceeded due to protocol amendments resulting from dose changes.

The first 6-10 subjects enrolled in each age cohort underwent serial PK sampling following single dose administration to guide selection of a regimen for chronic dosing (single dose visit [SDV]). These subjects underwent another serial PK sampling following repeat dose administration to further guide individualized dosing and to select a chronic dosage regimen for subsequently enrolled subjects in the same age cohort. Subsequently enrolled subjects then entered the study directly at the revised dosing regimen. The figures below display the study design schema for Cohort 1A and Cohort 2a, respectively.

Study APV20002 Schema (Cohort 1A)



Study APV20002 Schema (Cohort 2A)



Key Inclusion Criteria

- Male or female 4 weeks to <2 years of age
- Screening plasma HIV-1 RNA level ≥400 copies/mL
- Subjects who are able to construct an active NRTI backbone regimen consisting of 2 NRTIs (based on investigator's opinion and following viral resistance testing, if conducted)
- Subjects must be therapy-naïve or PI-naïve subjects (defined as having received less than one week of any PI) or subjects must be PI-experienced subjects (defined as having prior experience with no more than three PIs).

Key Exclusion Criteria

- Prior history of having received Agenerase (AGN)
- NNRTI therapy within 14 days prior to study drug administration or anticipated need for concurrent NNRTI therapy during the study period
- Protease inhibitor therapy within 5 days prior to study drug administration (applicable only for those subjects undergoing single dose visits)
- Grade 3 or higher (>5 x ULN) serum ALT and/or AST within 28 days prior to study drug administration and/or clinically relevant hepatitis within the previous 6 months.
- Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 28 days of study drug administration
- Treatment with immunomodulating agents or any agent with known anti-HIV activity (e.g., hydroxyurea or foscarnet) within 28 days of study drug administration
- Treatment with any of the following medications within 28 days prior to receiving study medication or the anticipated need during the study:
    - Drugs excluded for safety reasons: amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, dihydroergotamine, encainide, ergonovine, ergotamine, estazolam, flecainide, flurazepam, lovastatin, meperidine, methylergonovine, midazolam, pimozide, piroxicam, propafenone, propoxyphene, quinidine, simvastatin, terfenadine, and triazolam

    - Drugs excluded because they have the potential to decrease plasma protease inhibitor concentration: carbamazepine, dexamethasone, phenobarbital, primidone, rifampin, and St. John's Wort
- Treatment with other investigations drugs/therapies within 28 days prior to receiving study medication
- Known hypersensitivity to any study medications

Formulation(s) Used
FPV 50 mg/mL oral suspension; RTV 80 mg/mL oral solution

Background antiretroviral therapy (NRTIs) options provided by the Applicant: abacavir (ABC) 20 mg/mL oral solution (recommended dose is 8 mg/kg BID up to a max. of 600 mg/day) and lamivudine (3TC) 10 mg/mL oral solution (recommended dose is 4 mg/kg BID up to a max. of 300 m/day).

Subjects unable to utilize ABC and/or 3TC due to their resistance profile or who at the investigator's discretion would not use ABC and/or 3TC, obtained their background NRTIs via prescription.

Dosage and Administration
Both FPV oral suspension and RTV oral solution were measured and administered via separate dosing syringes. The FPV oral suspension was to be rigorously shaken prior to measuring for at least 20 seconds. Electronic timers were provided to parents/guardians of subjects in the study to assist with the accurate measurement of the time of shaking. Both FPV oral suspension and RTV oral solution were to be administered with food in order to enhance adherence through taste masking and to improve tolerability.

Reviewer Comment:
Although it was instructed to administer the FPV/RTV dose with food, on PK days and other study days many doses were not administered with food. This could be contributing to the degree of pharmacokinetic variability seen in this study. The lack of administration of the dose with food appeared to equally distributed across age groups in this study and was not seen more frequently in one age group versus another.

If vomiting or spitting up occurred within 30 minutes of administration, parents/guardians were instructed to re-administer the dose. Study drug was administered at the site on single dose visits (SDV) and on serial PK visits. All other doses were administered on an out-patient basis. The dose of the study drugs were adjusted throughout the study as subjects' weight increased. Dose adjustments were to occur when the dose would change by ≥10% from the subject's prior calculated dose.

Rationale for Dose Selection
Dose selection for this study was based on achieving plasma amprenavir (APV) PK exposures similar to those achieved with the FPV/RTV 700/100 mg BID dose in adults. The table below summarizes the plasma amprenavir PK targets:

PK Visit	Plasma APV PK Target	Basis for Target
Single dose FPV	AUC(0-∞) ≥16.8 µg·h/mL	25th percentile observed in HIV-infected adults receiving FPV 1395 mg BID
Single dose FPV/RTV	Concentration at 12 hours (C12) ≥0.24 µg/mL	25th percentile observed in healthy adults receiving FPV/RTV 700/100 mg
Repeat dose FPV/RTV BID	**Lower**: Cτ ≥1.48 µg/mL **Upper**: AUC(0-τ) >61.68 µg·h/mL Cτ >3.52 µg/mL	25th percentile observed in healthy adults receiving FPV/RTV 700/100 mg BID 95th percentile observed in healthy adults receiving FPV/RTV 700/100 mg BID

Fosamprenavir has not been previously studied in pediatric subjects less than 2 years of age, therefore evaluation of APV PK following single dose administration of FPV was implemented in a select number of subjects in order to inform the selection of individualized FPV/RTV regimens for repeat dosing for those subjects. This data was utilized to select a chronic FPV/RTV dosing regimen for subsequent subjects in the study. Since doses were chosen empirically, many dose modifications were made throughout the conduct of the study. The table below summarizes the doses changes and the rationale for each age cohort:

Age Cohorts	Original	Amendment 3	Amendment 5	Amendment 7	Amendment 8
1A (6 months to < 2 years)	SDV 1 30 mg/kg (N=10), SDV2 30/6 mg/kg (N=9), then individualized regimens ranging from FPV 30 to 45/RTV 6 to7 mg/kg BID (N=8)	45/7 mg/kg BID (subsequently enrolled subjects initiated multiple dosing from baseline) Prelim. data (N=5) suggested APV exposures following 45/7 mg/kg dose were low	45/7 mg/kg BID, then 60/7 mg/kg BID from Wk 2 Prelim. data (N=16) indicated exposures were w/ a dose of 45/7 mg/kg were closer to adult target exposures		45/7 mg/kg BID with not increase at Wk 2
2A (4 weeks to <6 months)	In order to align with dosing in Cohort 1, no subjects in Cohort 2 underwent SDV 1 30 mg/kg and SDV 2 30/6 mg/kg BID		SDV 45/7 mg/kg (N=11), then individualized dosing regimens ranging from FPV 30 to 60/RTV 7 to 10 mg/kg BID Prelim. data indicated a dose of 45/7 mg/kg resulted in lower APV Cτ and RTV Cτ as compared to adults	45/10 mg/kg BID	

The original single doses of FPV 30 mg/kg and FPV/RTV 30/6 at SDV1 and SDV2, respectively were selected based on: (1) what was known regarding APV PK in children, (2) conversion of APV to FPV dosing, and (3) taking into account known food effects on FPV oral suspension. Agenerase (amprenavir) 20 mg/kg BID was approved for use in children 4 to 16 years old (13 to 16 year olds weighing less than 50 kg). Unboosted FPV 23 mg/kg and APV 20 mg/kg are equivalent in amprenavir content, and equimolar doses of FPV and APV have been shown to deliver comparable plasma APV exposures in adults. Administration of FPV oral suspension with food results in a 28% reduced plasma $APV_{0-\infty}$. Therefore, the FPV dose was adjusted for the food effect by increasing the unboosted FPV dose from 23 mg/kg BID to 30 mg/kg BID.

The SDV2 dose of FPV/RTV 30/6 mg/kg was selected because it has been evaluated as part of a once daily regimen in pediatric subjects 2 to 18 years old (Study APV20003). It should be noted that no subjects in Cohort 2A underwent SDV1 30mg/kg or SDV 2 30/6 mg/kg PK sampling. Instead, PK samples were collected in an initial few subjects in the 4 weeks to <6 months old age cohort following single dose administration of FPV/RTV 45/7 mg/kg (as documented in Protocol Amendment 5).

Assessments

Pharmacokinetics
For subjects in Cohort 1A, plasma PK samples were collected at 0, 1, 2, 4, 6, 8, and 12 hours post dosing of SDV1 and at 2 and 12 hours post dosing of SDV2. Prior to Amendment 5 of the protocol, subjects enrolled in Cohort 1A underwent serial plasma PK sampling at 0, 1, 2, 4, 6, 8, and 12 (optional) hours post dosing at Week 2. From Amendment 5 onward, subjects enrolled in Cohort 1A underwent abbreviated PK sampling at 0, 2, and 4 hours post dosing at Week 2 and full PK sampling at 0, 1, 2, 4, 6, 8 and 12 (optional) hours post dosing at Week 8.

For subjects in Cohort 2A, plasma PK samples were collected at 0, 1, 2, 4, 6, 8, and 12 (optional) hours post dosing of FPV/RTV at Week 2.

In addition, all subjects had one plasma PK sample collected immediately prior to dosing (trough sampling) on Weeks 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.

Safety
Hematology and clinical chemistry labs were evaluated at the Screening visit, Day 1, and Weeks 4, 12, 24, 36, 48, every 12 weeks thereafter, and at Withdrawal. Lipid measurements were collected at Day 1, Weeks 24 and 48, every 12 weeks thereafter, and at Withdrawal. Serum lipase and serum α 1-acid glycoprotein (AAG) were also measured throughout the study. Clinical adverse events (AEs), concurrent medications/blood products and background ART information were collected at Single Dose Visit, Day 1, and Weeks 2, 4, 8, 12, 16, 24, 36, 48, every 12 weeks thereafter, and at Withdrawal.

Efficacy
Antiviral response assessments included quantitative plasma HIV-1 RNA levels; lymphocyte subsets (including total lymphocytes; absolute and percent CD4+ and CD8+ cell counts); HIV associated conditions; and genotypic HIV-1 resistance testing. All evaluations were performed at Screening, Day 1 and at Weeks 4, 12, 24, 36, 48, every 12 weeks thereafter, and at Withdrawal.

Statistical Methods

Pharmacokinetics
The following single dose plasma APV PK parameters were estimated: C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, CL/F, $t_{1/2}$, and the apparent terminal phase rate constant (λz). The following steady-state plasma APV and RTV PK parameters were estimated: C_{max}, T_{max}, $AUC_{0\text{-}\tau}$, $AUC_{(0\text{-}\tau)/\tau}$, and C_{τ}. Analysis of variance (ANOVA), considering study population as a fixed effect, was performed to compare log-transformed plasma APV and RTV CL/F between pediatric subjects and historical adult data, using SAS (Version 9.1) Mixed Linear Model procedure. Results from these analyses were exponentiated to obtain a point estimate and 90% confidence interval (CI) estimate of the test (pediatric)-to-reference (historical adult) ratio of geometric least squares

(GLS) means. An additional ANOVA was performed, using the same methods, to compare plasma APV $AUC_{0-\tau}$, C_{max}, and C_{τ} between pediatric subjects receiving FPV/RTV 45/7 mg/kg BID and the historical adult data.

Safety

Exposure to study medication, measured by the number of weeks on study drug, was summarized. The proportion of subjects reporting adverse events was tabulated. Incidence and severity of all AEs/SAEs, treatment related AEs, AEs leading to withdrawal and SAEs were summarized.

Laboratory data and vital signs (absolute values and change from Baseline) were summarized by visit. In addition, the number and percentage of subjects with laboratory values of clinical concern was summarized.

Efficacy

Secondary analyses at each visit included: the proportion of subjects with plasma HIV-1 RNA <400 copies/mL at each visit, proportion of subjects with plasma HIV-1 RNA <50 copies/mL, change from Baseline in plasma HIV-1 RNA at each study visit, proportion of subjects with ≥1.0 log_{10} decrease in plasma HIV-1 RNA at each study visit, change from Baseline in the percentage of CD4+ lymphocytes at each study visit. All key secondary endpoints were summarized (by visit where applicable).

Results

A total of 59 subjects received at least one dose of investigation product in Study APV20002. Five subjects only received single doses only were not included in the ITT(E) population, but were included in the safety population. Fifty-four subjects received repeated dosing of FPV/RTV BID in this study and were included in the ITT(E) population. The table below summarizes the baseline demographic characteristics of the ITT(E) population overall and by age cohort:

	FPV/RTV BID		
	4 weeks to <6 months N=26	6 months to <2 years N=28	Total (N=54)
Age (months), median (range)	3 (2, 5)	13 (6, 24)	6 (2, 24)
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 (17)
Non-Hispanic or Latino	26 (100)	19 (68)	45 (83)

Subjects weight ranged from 3.2 to 7.8 kg in the 4 weeks to <6 month age cohort and from 4.9 to 12.1 kg in the 6 months to <2 years age cohort. The majority of subjects in the study were of Black race (81%), 2 were Caucasian, and 8 were classified as Other. Forty-four of the total subjects were enrolled in South Africa, 8 in Mexico, and one each in Argentina and Portugal. Sixty-five percent of the subjects had baseline HIV-1 RNA levels > 250,000 copies/mL with a median plasma HIV-1 RNA level of 5.6 log_{10} copies/mL. Of the 54 subjects, 89% has a baseline CD4+ cell count of ≥500 cells/mm^3 and 46% had percent CD4+ cell counts <25%. Of the 54

subjects in the study, 17 were treatment naïve to any ART. The following table summarizes the prior ART by PI status for the ITT(E) population:

		FPV/RTV BID	
Antiretroviral Therapy Class		PI-naive (N=49) n (%)	PI-experienced (N=5) n (%)
Any Antiretroviral Therapy		32 (65)	5 (100)
Number of NRTIs taken	1	27 (55)	0
	2	2 (4)	5 (100)
	3	1 (2)	0
Number of NNRTIs taken	1	29 (59)	1 (20)
Number of PIs taken	1	0	4 (80)
	2	0	1 (20)[a]

Twenty-seven of the 30 subjects with prior NNRTI use took drug for just one day and in each case the drug was nevirapine (it is assumed that this was a single dose given at birth). For those with prior PI exposure, the median duration was 39 weeks. The following table lists the prior NRTIs, NNRTIs, and PIs taken and duration of exposure by PI status for the ITT(E) population:

	FPV/RTV BID	
	PI-naive (N=49)	PI-exp. (N=5)
NRTIs, n (%)		
Median (IQR) duration of exposure (weeks)	1 (1, 4)	39 (16, 64)
ABACAVIR	1 (2)	0
DIDANOSINE	0	1 (20)
LAMIVUDINE	3 (6)	5 (100)
STAVUDINE	0	2 (40)
ZIDOVUDINE	30 (61)	2 (40)
NNRTIs, n (%)		
Median (IQR) duration of exposure (weeks)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
NEVIRAPINE	29 (59)	1 (20)
PIs, n (%)		
Median (IQR) duration of exposure (weeks)	0	39 (16, 64)
LOPINAVIR/RITONAVIR	0	2 (40)
NELFINAVIR	0	3 (60)

All subjects receiving FPV/RTV BID also received background ART. NNRTI and PI use was prohibited during the study. Initially, 42 (78%) subjects received ABC and 3TC, 5 (9%) subjects received 3TC and ZDV. Two subjects changed NRTIs during the study. The following table summarizes the concomitant ART use by PI status for the ITT(E) population:

ATC Level 4 Medication	FPV/RTV BID	
	PI-naive (N=49) n (%)	PI-exp. (N=5) n (%)
LAMIVUDINE	47 (96)	0
ABACAVIR	44 (90)	2 (40)
ZIDOVUDINE	8 (16)	5 (100)
DIDANOSINE	1 (2)	3 (60)
STAVUDINE	2 (4)	0

None of the components of the various background ARTs would be anticipated to have a significant PK interaction with amprenavir or RTV.

Bioanalytical

The methods and bioanalysis of FPV, APV, and RTV are acceptable. Concentrations of FPV, APV, and RTV in plasma samples collected during the study were determined using Good Laboratory Practice (GLP) methods and validated liquid chromatography with tandem mass spectroscopy (HPLC/MS/MS) bioanalytical methods. The assays were performed by (b) (4) . All samples were analyzed in the timeframe supported by frozen stability storage data. The long-term stability data for RTV of 600 days and FPV and APV of 836 days (at -20˚C) covers the duration of long-term stability data necessary for Study APV20002.

The lower limit of qualification (LLQ) and upper limit of qualification (ULQ) for FPV were 5 ng/mL and 100 ng/mL and for APV and RTV were 10 ng/mL and 10,000 ng/mL, respectively. Calibration curves were obtained using a linear regression algorithm with 1/concentration weighing of the peak area ration of analyte to internal standard. All coefficients (r) for FPV (GW433908), APV (GW141W94), and RTV (GW278007A) were greater than 0.99. The assay performance for Study APV20002 is shown in the table below:

Assay Performance for Study APV20002		
Total Runs (		
GW141W94	Accepted Runs 125	Rejected Runs 9
QC Samples	Precision (%CV)* 4.5 to 7.4%	Accuracy (%Dev)* -4.1 to -2.0%
	*Based on QC1, QC2, and QC3 results from accepted runs.	
Calibration Standards	Precision (%CV) 3.3 to 6.1%	Accuracy (%Dev) -2.9 to 1.5%
GW433908	Accepted Runs 118	Rejected Runs 22
QC Samples	Precision (%CV)* 7.7 to 10.7%	Accuracy (%Dev)* -2.3 to -1.0%
	*Based on QC1, QC2, and QC3 results from accepted runs.	
Calibration Standards	Precision (%CV) 4.9 to 6.8%	Accuracy (%Dev) -0.7 to 1.3%
GW278007A	Accepted Runs 112	Rejected Runs 15
QC Samples	Precision (%CV)*	Accuracy (%Dev)*
	*Based on QC1, QC2, and QC3 results from accepted runs.	
Calibration Standards	Precision (%CV) 4.4 to 7.1%	Accuracy (%Dev) -1.0 to 0.6%

Pharmacokinetics

The following table summarizes the steady-state plasma APV PK parameters and statistical comparisons for FPV/RTV BID in the 4 weeks to <6 months old age group and historical adults:

Plasma APV PK Parameter	4 Weeks to <6 Months[a]		Historical Adult 700/100 mg BID[a,c,d] N=79	4 Weeks to <6 months vs. Historical Adults[b,d]	
	45/10 mg/kg BID N=9[c]	60/10 mg/kg BID N=3[c]		45/10 mg/kg BID	60/10 mg/kg BID
AUC(0-τ) (h·µg/mL)	26.6 (15.2, 46.8) [84]	47.2 (19.9, 112) [36]	37.0 (35.1, 38.9) [33]	0.720 (0.542, 0.957)	1.28 (0.786, 2.08)
Cmax (µg/mL)	6.25 (3.82, 10.2) [71]	10.8 (7.25, 16.2) [16]	5.62 (5.35, 5.92) [33]	1.11 (0.853, 1.45)	1.93 (1.22, 3.04)
Cτ (µg/mL)	0.860 (0.500, 1.48) [96]	1.99 (0.892, 4.44) [54]	2.17 (2.05, 2.30) [38]	0.397 (0.305, 0.516)	0.918 (0.619, 1.36)

a. Geometric Mean (95% CI) [CVb%]
b. GLS Mean Ratio (90% CI)
c. N=16 for 45/10 mg/kg BID Cτ, N=4 for 60/10 mg/kg BID Cτ, N=158 for historical adult AUC(0-τ)
d. Healthy Adults

The following table summarizes the steady-state plasma APV PK parameters and statistical comparisons for FPV/RTV BID in the 6 months to <2 year old age group and historical adults:

Plasma APV PK Parameter	6 Months to <2 Years[a]		Historical Adult 700/100 mg BID[a,c,d] N=79	6 months to <2 Years vs. Historical Adults[b,d]	
	45/7 mg/kg BID N=10[c]	60/7 mg/kg BID N=9[c]		45/7 mg/kg BID	60/7 mg/kg BID
AUC(0-τ) (h·µg/mL)	27.5 (14.5, 52.1) [110]	48.4 (12.9, 181) [334]	37.0 (35.1, 38.9) [33]	0.744 (0.568, 0.975)	1.31 (0.969, 1.77)
Cmax (µg/mL)	5.84 (3.35, 10.2) [91]	10.4 (3.64, 30.0) [235]	5.62 (5.35, 5.92) [33]	1.04 (0.807, 1.34)	1.86 (1.43, 2.42)
Cτ (µg/mL)	1.99 (1.56, 2.53) [68]	2.76 (1.70, 4.47) [89]	2.17 (2.05, 2.30) [38]	0.917 (0.772, 1.09)	1.27 (0.989, 1.64)

a. Geometric Mean (95% CI) [CVb%]
b. GLS Mean Ratio (90% CI)
c. N=28 for 45/7 mg/kg BID Cτ, N=12 for 60/7 mg/kg BID Cτ, N=158 for historical adult AUC(0-τ)
d. Healthy Adults

Inspection Results

The Office of Scientific Investigations was requested to conduct inspections of three of the higher enrolling clinical sites that collected PK data (Center #93702 South Africa; Center #37503 Mexico City; Center #37504 Mexico City) and the bioanalytical laboratory that analyzed the FPV, APV, and RTV plasma samples (b) (4). Following these inspections, no significant objectionable conditions were observed and Form FDA-483 was not issued. The OSI Reviewer concluded that the PK data from the clinical and bioanalytical portions of the study are acceptable for Agency review (see DSI Consult – Bioequivalence Establishment Inspection Report authored by Dr. Young Moon; dated 03/26/12).

Safety

Fifty-nine subjects were included in the safety population. Fifty-four subjects received FTV/RTV BID on a chronic basis with the median time of exposure being 573.5 days. Overall, 92% of the safety population reported at least 1 treatment-emergent AE regardless of causality. The system organ class (SOC) with the highest incidence of AEs was infections and infestations (88%), gastrointestinal disorders (59%), and skin and subcutaneous tissue disorders (36%). The most common treatment-emergent AEs (≥5%) were diarrhea (47%), upper respiratory tract infection (34%), and gastroenteritis (31%).

Three deaths were reported during the study: (1) Subject 7156 – 24 month old male died (b) (6) days after receiving a single dose of FPV and (b) (6) days after receiving a single dose of FPV/RTV – developed acute abdomen of unknown origin (not considered to be related to investigational product; (2) Subject 8611 – 19 month old female died on day (b) (6) of the study – experienced a Grade 4 septicemia (not considered to be related to the investigational product); (3) Subject 8641 – 2 month old male died on day (b) (6) of the study – developed Grade 4 drug-related gastroenteritis on day (b) (6) of the study.

Overall the adverse event profile of FPV and FPV/RTV in patients 4 weeks to <2 years old was similar to that of older pediatric patients and adults. However, vomiting with FPV and FPV/RTV regardless of causality did occur in all pediatric age cohorts studied more frequently than in adults.

Efficacy

Of the 54 subjects receiving FPV/RTV BID dosing (the majority of who were PI-naïve) in Study APV20002, 72% achieved HIV-1 RNA less than 400 copies/mL at Week 24. As a comparison, PI-naïve subjects receiving FPV/RTV BID in study APV29005, 71% achieved HIV-1 RNA less than 400 copies/mL at Week 24.

In Study APV20002, the median increases from baseline in CD4+ cell counts were 400 cells/mm3 in patients aged 4 weeks to <6 months and 278 cells/mm3 in patients aged 6 months to <2 years. The median percent changes from baseline in CD4+ count were 7% in patients aged 4 weeks to <6 months and 6% in patients aged 6 months to <2 years.

Conclusion

FPV/RTV was generally well tolerated in children <2 years of age. FPV/RTV 45/7 mg/kg BID achieved plasma APV exposures in subjects 6 months to <2 years that were comparable to APV exposures achieved in adults receiving FPV/RTV 700/100 mg BID. Exposures achieved in PI-naïve patients 4 weeks to <6 months age receiving FPV/RTV 45/10 mg/kg were lower than adults receiving FPV/RTV 700/100 mg BID, but were similar to exposures observed in treatment-naïve adults receiving FPV/RTV 1400/100 mg QD. No PI-experienced subjects less than 6 months of age were evaluated in this trial. Both age cohorts had similar clinical outcomes at 24 weeks and demonstrated a safety profile that was similar to that seen in older children and adults.

5 APPENDIX

5.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Do the [redacted] (b) (4) fosamprenavir/ritonavir (FPV/RTV) pediatric dosing [redacted] (b) (4) provide exposures similar to safe and effective exposures in adults?

Amprenavir (APV) exposures following FPV/RTV BID dosing were evaluated in protease-inhibitor (PI)-naïve and –experienced pediatrics at least 4 weeks to 2 years in APV20002 and 2 years to 6 years in APV290005. Intensive PK sampling was performed in 14 pediatrics 2-<6 years at a dose of FPV/RTV 23/3 mg/kg BID. APV exposures ($AUC_{(0-\tau)}$, C_{max}, and C_{τ}) all exceeded values from historical adults administered 700/100 mg FPV/RTV BID by 50-66% (Table 1) . However, these higher exposures were deemed acceptable based on the comparable efficacy results (viral load <400 copies/mL) between APV29005 (65%; 18 PI-naïve and 2 PI-experienced) and adults (69% for PI-naïve administered 1400/200 mg QD and 58% for PI-experienced administered 700/100 mg BID) and similar safety observations to that in adults.

Table 1: Comparison Between APV Exposures in Pediatrics 2-<6 Years and Adults

Plasma APV PK Parameter	2 to <6 Years[a,c] 23/3 mg/kg BID N=14	Historical Adult 700/100 mg BID[a,c,d] N=159	2 to <6 Years vs. Historical Adult[b,d]
AUC(0-τ) (h.µg/mL)	55.3 (37.9, 80.7) [73]	37.0 (35.1, 38.9) [33]	1.50 (1.27, 1.77)
Cmax (µg/mL)	8.66 (6.08, 12.3) [67]	5.62 (5.35, 5.92) [33]	1.54 (1.30, 1.82)
Cτ (µg/mL)	3.59 (2.60, 4.97) [64]	2.17 (2.05, 2.30) [38]	1.66 (1.35, 2.04)

Likewise, intensive PK sampling was performed in 19 pediatrics from APV20002 administered either FPV/RTV 45/7 mg/kg BID (n=10) or FPV/RTV 60/7 mg/kg BID (n=9). APV exposures ($AUC_{(0-\tau)}$, C_{max}, and C_{τ}) for pediatrics administered 45/7 mg/kg were similar to that attained by adults while exposures at 60/7 mg/kg BID exceeded all adult exposures (Table 2). The higher C_{max} for FPV/RTV was a concern due to exceeding that observed in adults with 1400/200 mg QD. This pediatric age group included 23 PI-naïve and 5 PI-experienced pediatrics with 71% achieving viral load <400 copies/mL, which was comparable to the efficacy in adults.

Table 2: Comparison Between APV Exposures in Pediatrics 6 Months to <2 Years and Adults

Plasma APV PK Parameter	6 Months to <2 Years[a]		Historical Adult 700/100 mg BID[a,c,d] N=79	6 months to <2 Years vs. Historical Adults[b,d]	
	45/7 mg/kg BID N=10[c]	60/7 mg/kg BID N=9[c]		45/7 mg/kg BID	60/7 mg/kg BID
AUC(0-τ) (h·µg/mL)	27.5 (14.5, 52.1) [110]	48.4 (12.9, 181) [334]	37.0 (35.1, 38.9) [33]	0.744 (0.568, 0.975)	1.31 (0.969, 1.77)
Cmax (µg/mL)	5.84 (3.35, 10.2) [91]	10.4 (3.64, 30.0) [235]	5.62 (5.35, 5.92) [33]	1.04 (0.807, 1.34)	1.86 (1.43, 2.42)
Cτ (µg/mL)	1.99 (1.56, 2.53) [68]	2.76 (1.70, 4.47) [89]	2.17 (2.05, 2.30) [38]	0.917 (0.772, 1.09)	1.27 (0.989, 1.64)

a. Geometric Mean (95% CI) [CVb%]
b. GLS Mean Ratio (90% CI)
c. N=28 for 45/7 mg/kg BID Cτ, N=12 for 60/7 mg/kg BID Cτ, N=158 for historical adult AUC(0-τ)
d. Healthy Adults

Finally, intensive PK sampling was performed in 12 pediatrics at least 4 weeks to <6 months from APV20002 administered either FPV/RTV 45/7 mg/kg BID (n=9) or FPV/RTV 60/7 mg/kg BID (n=3). APV exposures ($AUC_{(0-\tau)}$, C_{max}) for pediatrics administered 45/7 mg/kg were similar to that attained by adults, though C_τ was 60% lower. AUC and C_τ exposures for 60/10 mg/kg were similar to adults while C_{max} was 2-fold higher (Table 3). As before, the higher C_{max} for FPV/RTV 60/10 mg/kg BID was a concern due to exceeding that observed in adults with FPV/RTV 1400/200 mg QD. This pediatric age group included 29 PI-naïve pediatrics with 73% achieving viral load <400 copies/mL, which was comparable to the efficacy in adults. Of note, this is the pediatric group with the lowest C_τ and included no PI-experienced pediatrics.

Table 3: Comparison Between APV Exposures in Pediatrics At Least 4 Weeks to 6 Months and Adults

Plasma APV PK Parameter	4 Weeks to <6 Months[a]		Historical Adult 700/100 mg BID[a,c,d] N=79	4 Weeks to <6 months vs. Historical Adults[b,d]	
	45/10 mg/kg BID N=9[c]	60/10 mg/kg BID N=3[c]		45/10 mg/kg BID	60/10 mg/kg BID
AUC(0-τ) (h·µg/mL)	26.6 (15.2, 46.8) [84]	47.2 (19.9, 112) [36]	37.0 (35.1, 38.9) [33]	0.720 (0.542, 0.957)	1.28 (0.786, 2.08)
Cmax (µg/mL)	6.25 (3.82, 10.2) [71]	10.8 (7.25, 16.2) [16]	5.62 (5.35, 5.92) [33]	1.11 (0.853, 1.45)	1.93 (1.22, 3.04)
Cτ (µg/mL)	0.860 (0.500, 1.48) [96]	1.99 (0.892, 4.44) [54]	2.17 (2.05, 2.30) [38]	0.397 (0.305, 0.516)	0.918 (0.619, 1.36)

a. Geometric Mean (95% CI) [CVb%]
b. GLS Mean Ratio (90% CI)
c. N=16 for 45/10 mg/kg BID Cτ, N=4 for 60/10 mg/kg BID Cτ, N=158 for historical adult AUC(0-τ)
d. Healthy Adults

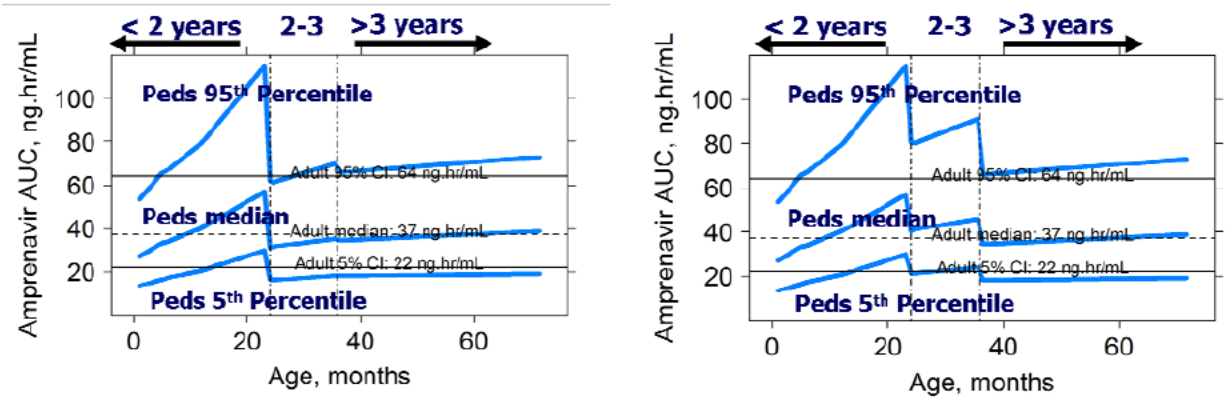
Overall, the doses recommended by the sponsor of 45/7 mg/kg in pediatrics (b) (4) and 23/3 mg/kg in pediatrics (b) (4) provide comparable efficacy, safety and exposures to that achieved in adults. (b) (4)

1.1.2 Is the dose FPV/RTV 30/3 mg BID for pediatrics [redacted] supported by modeling and simulation?

An increase FPV/RTV from 23/3 mg/kg BID to 30/3 mg/kg BID [redacted] the sponsor's final model results for a subgroup of pediatrics <3 years, though additional suggests that the dosing [redacted] could be extended to pediatrics >18 months.

Shown below are the simulations based on the sponsor's model for pediatrics at least 4 weeks to <6 years for [redacted] age-band dosing (left) and updated dosing [redacted] administering pediatrics 2-<3 years 30/3 mg/kg BID instead of 23/3 mg/kg BID (right). The modeling and simulation results [redacted] pediatrics <3 years may require higher FPV/RTV dosing to achieve similar exposures to that of adults and other pediatrics. However, the results also indicate that the 30/3 mg/kg BID dosing [redacted] could be further extended to pediatrics <2 years. This observation motivated the exploration of weight-band dosing (Question 1.3).

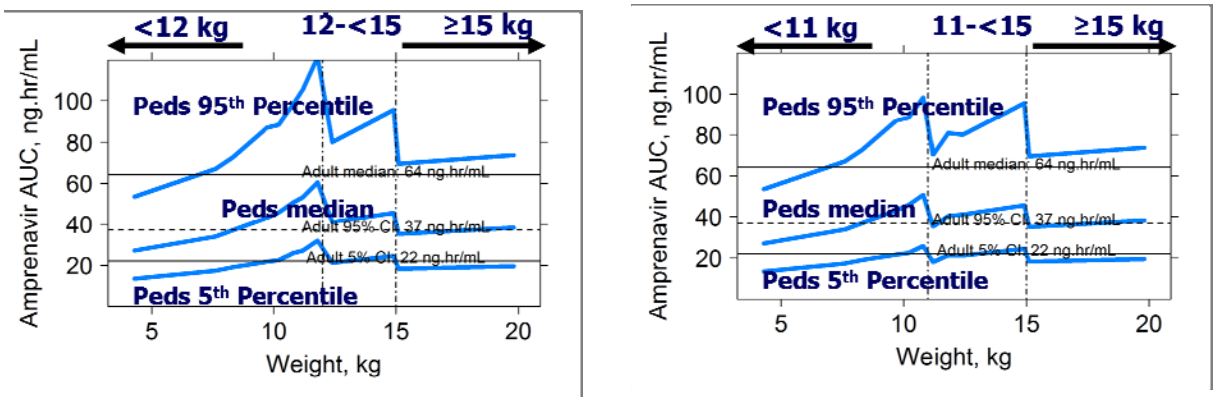
Figure 1: Simulated Pediatric AUC for the [redacted] Age- Band Dosing in Table 4 Using the Sponsor's Final Model



[redacted]

weights for pediatrics 3 to <6 years ranged between 14 to kg) and simulations based on the sponsor's modeling and simulation results (Figure 2). As before, the selected dosing bands indicate higher exposures at the transition from FPV/RTV 30/3 mg/kg BID to 45/7 mg/kg and that the 30/3 mg/kg BID weight-band could be extended to lower body weights. Simulations using 30/3 mg/kg BID for pediatrics 11-<15 kg are shown in Figure 2 (right) demonstrating that the weight-band can be extended to 11-<15 kg while maintaining exposures similar to adults.

Figure 2: Simulated Pediatric AUC for (b) (4) Weight Band Dosing in Table 4 Using the Sponsor's Final Model



1.1.4 Is the information in pediatrics <6 months sufficient to support FPV/RTV 45/7 mg/kg BID?

The modeling and simulation results, observed APV PK, and pediatrics included in APV20002 supports administration of FPV/RTV 45/7 mg/kg BID to PI-naïve pediatrics at least 4 weeks to <6 months. However, the results are insufficient to support BID dosing in PI-experienced pediatrics <6 months.

As shown above in Table 3, the C_τ for pediatrics <6 months was 60% than that observed in adults administered FPV/RTV 700/100 mg BID, the only FPV regimen approved for PI-experienced patients. (b) (4) FPV/RTV 1400/200 mg QD was based on results from APV30003 (PI-experienced adult trial) that demonstrated a lower response with FPV/RTV QD compared to FPV/RTV BID (50% and 37% of patients <400 and <50 copies/mL for QD compared to 58% and 46% of patients <400 and <50 copies/mL for BID). The main difference between the QD and BID treatment arms was C_τ suggesting this was the primary exposure parameter for efficacy. Likewise, dosing increases in a small subset of pediatrics <6 months suggested that C_{max} may exceed that observed in adults. Finally, different dosing intervals, such as TID, were considered but ultimately rejected due to practical concerns.

As a next analysis, the exposures in pediatrics <6 months were compared to the observed exposures in adults for all approved regimens. Of the approved adult regimens, the pediatric exposures for AUC, C_{max}, and C_τ were most similar to FPV/RTV 1400/100 QD, a regimen that is only approved for PI-naïve patients (Table 5). Also, the modeling and simulation results that suggest even lower C_τ in pediatrics at least 4 weeks to 2 months and it was observed that no PI-experienced patients were included in APV20002

(youngest patient was 2 months at baseline and 11 weeks at PK sampling). Based on these observations, it was concluded that FPV/RTV 45/7 mg/kg was suitable for PI-naïve pediatrics at least 4 weeks to <6 months. However, there was insufficient data to support dosing in PI-experienced pediatrics <6 months.

Table 5: Comparison Between APV Exposures in Pediatrics At Least 4 Weeks to 6 Months and All Approved Adult FPV/RTV Regimens

Plasma APV PK Parameter	45/10 mg/kg BID (n=9)	Ratio to adult (700/100 mg BID)	Ratio to adult (1400/200 mg QD)	Ratio to adult (1400/100 mg QD)
AUC_{24} (h·µg/mL)	53.2	0.72	0.77	0.80
C_{max} (µg/mL)	6.3	1.11	0.88	0.80
C_{τ} (µg/mL)	0.86	0.40	0.59	1.00

1.2 Recommendations

The recommended dosage of FPV/RTV for PI-naïve pediatrics >1 month and treatment-experienced pediatrics >6 months at the following doses is shown below:

Weight	
< 11 kg	LEXIVA 45 mg/kg plus ritonavir 7 mg/kg[a]
11 kg - <15 kg	LEXIVA 30 mg/kg plus ritonavir 3 mg/kg[a]
15 kg - <20 kg	LEXIVA 23 mg/kg plus ritonavir 3 mg/kg[a]
≥20 kg	LEXIVA 18 mg/kg plus ritonavir 3 mg/kg[a]

[a] When dosing with ritonavir, do not exceed the adult dose of LEXIVA 700 mg/ritonavir 100 mg twice daily dose.

There was insufficient data to support dosing of FPV/RTV in PI-experienced pediatrics <6 months.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

1 INDICATIONS AND USAGE

(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

2 PERTINENT REGULATORY BACKGROUND

The clinical pharmacology data presented in the original LEXIVA™ New Drug application (NDA) 21-548 supported dosing recommendations for administration of fosamprenavir (FPV) tablet formulation +/- ritonavir (RTV) boosting in Human Immunodeficiency Virus type 1 (HIV-1) infected adults. Subsequently, clinical pharmacology data presented in LEXIVA NDA 22-116 supported dosing recommendations for FPV suspension formulation as FPV/RTV in pediatric and adolescent subjects aged 6 to 18 years and FPV in pediatric and adolescent subjects aged 2 to 18 years. Dosing recommendations for these groups are shown below (Table 6):

Table 6: Approved LEXIVA Dosage Regimens for Adult and Pediatric Patients

Age Group	Treatment Naïve Patients	Treatment Naïve and Treatment Experienced Patients
Children 2 to 5 years	LEXIVA 30 mg/kg twice daily[1,2] (without ritonavir [RTV])	Not Approved
Children ≥6 years	LEXIVA 30 mg/kg twice daily[1,2] (without RTV)	LEXIVA 18 mg/kg twice daily Plus RTV 3 mg/kg[1,3]
Adults	LEXIVA 1400 mg twice daily (without RTV)	LEXIVA 700 mg twice daily Plus RTV 200mg twice daily
	LEXIVA 1400 mg once daily Plus RTV 100mg once daily	
	LEXIVA 1400 mg once daily Plus RTV 200mg once daily	

1. LEXIVA oral suspension should be administered with food in pediatric patients as was done in clinical studies.
2. Up to maximum dose of LEXIVA 1400 mg twice daily
3. Up to maximum dose of LEXIVA 700 mg twice daily plus RTV 100 mg twice daily

This supplemental NDA (sNDA) presents the clinical pharmacology data to extend dosing recommendations for FPV/RTV to pediatric subjects aged 4 weeks to <6 years. Specifically, dosing recommendations for the following patient groups are proposed (Table 7):

Table 7: Proposed LEXIVA/ritonavir Dosing Regimens for Pediatrics Patients <6 years old

(b) (4)

(b) (4)

The weight-bands proposed by the sponsor are listed below:

(b) (4)

3 RESULTS OF SPONSOR'S ANALYSIS

Population PK Model

Three Phase 2, 48-week, open-label, multinational clinical trials of FPV in pediatric HIV-infected patients contributed data for this population PK analysis. Each study was designed to evaluate the PK, safety, tolerability, and antiviral activity of FPV administered to HIV-infected pediatric subjects. Concurrent medications expected to alter plasma APV exposure were excluded from the studies, with the exception of RTV. Final data for Study APV20003 and data available for the interim 24-week analyses of Studies APV20002 and APV29005 were included in this population PK analysis (Table 8).

Table 8: Summary of Continuous Covariates and PK Samples for the Population PK Analysis

Covariate	APV20002 (N=51)	APV20003 (N=59)	APV29005 (N=102)	All (N=212)
	Median (min, max)	Median (min, max)	Median (min, max)	Median (min, max)
Age (months)	13 (2, 36)	118 (26, 234)	108 (24, 228)	84 (2, 234)
Weight (kg)	8.9 (3.9, 14.1)	32.3 (10.2, 101)	31.3 (9.9, 116)	24 (3.9, 116)
Height (cm)	72 (51, 93)	135 (82, 180)	132 (78, 190)	122 (51, 190)
BSA (m^2)	0.44 (0.25, 0.61)	1.10 (0.51, 2.25)	1.09 (0.49, 2.40)	0.92 (0.25, 2.40)
AAG (g/L)	0.85 (0.42, 4.37)	0.74 (0.36, 2.80)0.	0.78 (0.31, 2.53)	0.78 (0.31, 4.37)
Baseline Age (months)	6 (2, 24)	144 (23, 204)	108 (24, 216)	72 (2, 216)
Baseline Weight (kg)	6.6 (3.2, 11.1)	33.5 (10.3, 91.5)	29.7 (10.9, 103)	21 (3.2, 103)
Baseline Height (cm)	65 (49, 82)	142 (79, 180)	127 (78, 172)	116 (49, 180)
Baseline BSA (m^2)	0.36 (0.22, 0.52)	1.16 (0.50, 2.11)	1.04 (0.51, 2.24)	0.84 (0.22, 2.24)
Visits	313 (20%)	341 (22%)	902 (58%)	1556 (100%)
PK Samples	578 (24%)	518 (21%)	1350 (55%)	2446 (100%)

Source: Sponsor's Population PK Study Report, 2011N118856, pg 4

Base Model Development

Based on the results from previous population PK analyses in pediatric patients and adults a two-compartment model with first-order absorption and elimination was chosen as the structural model. Similar to previous reports, PK parameters were estimated using the FPV dose and not the equivalent APV dose. The starting base model incorporated an exponential inter-individual variability term on all PK parameters. Due to the known effects of weight on clearance and volume of distribution, standard allometric relationships (exponents of 0.75 for clearance and 1.0 for volume) were applied.

In the adult population PK model, the volume of distrubtion of the peripheral compartment (V3/F) was difficult to estimate and was fixed to (b) (4). In the previous pediatric population PK model, V3/F was estimated, although not very precisely. Therefore, several models were explored to compare the effect of fitting or fixing V3/F. It was decided to fix V3/F as models which fit V3/F and were otherwise the same resulted in an OFV that was increased or not significantly decreased. Once it was decided that V3/F should be fixed, values ranging from (b) (4) were tested to optimize the value of V3/F. A value of (b) (4) was selected for V3/F for consistency between this model and previous models and because most other models explored resulted in an increase in the OFV.

Models were explored to determine the optimal approach to handling doses that were partially vomited. It was decided that doses which were partially vomited should have a bioavailability fixed to 0.5. A model which fit the bioavailability to 1 for a partially vomited dose and a model which estimated the bioavailability for a partially vomited dose where also explore but neither model offered improvement over the selected model.

Covariate Model Development

The final model developed previously in pediatric subjects, with modifications due to currently available data, was the starting point for the current analysis. Model selection was driven by the data and based on evaluation of goodness-of-fit plots (observed vs predicted concentration, weighted residual vs. predicted concentration or time, histograms of individual random effects, etc.), successful convergence (with at least 3 significant digits in parameter estimates), plausibility and precision of parameter estimates, and the minimum OFV.

The following covariates were considered before starting the analysis: age, body weight, height, body surface area, alpha-1-acid glycoprotein, and RTV coadminstration. RTV significantly reduces APV clearance. Of the covariates considered before starting the analysis, AAG concentration and hepatitis status were not evaluated because the majority of subjects in Study APV20002 did not have this information collected. The effect of RTV was described using a categorical flag (0=without RTV; 1=with RTV) assuming a maximal inhibition at the doses included in the model, as has been described previously.

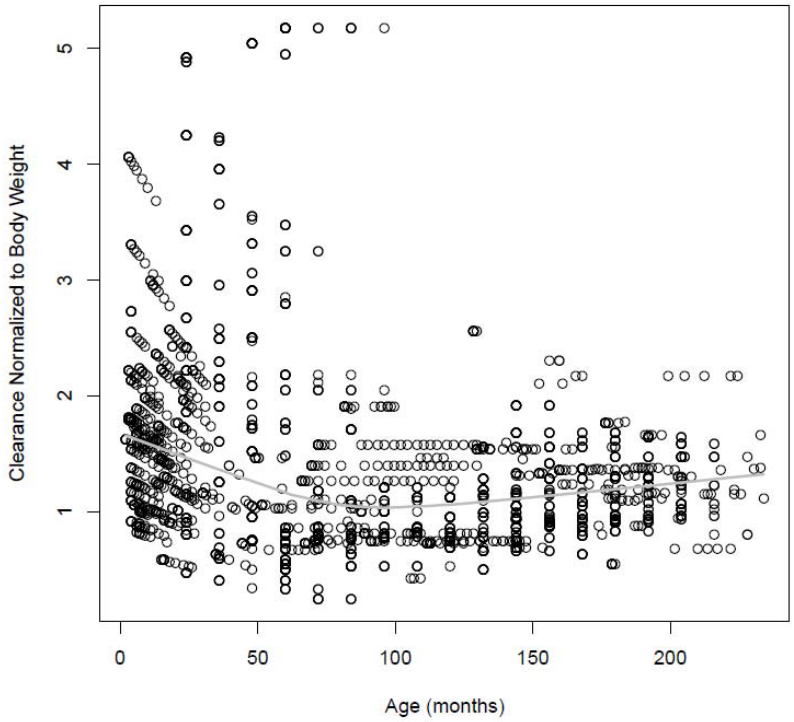
After identification of the base model, a full covariate model approach was implemented, where all covariate-parameter relationships of interest were entered in the model, and parameters were estimated. Plots of eta-covariate values were reviewed after each major run to ensure all possible covariate-parameter relationships were evaluated. The full model did not simultaneously include highly correlated covariates. For most continuous covariates, a power function was utilized

$$TVP_i = \theta_{TVP} * (COV_i/COVST)^{\theta 2}$$

where TVP_i is the PK parameter for an individual i with a COV_i value of the covariate, while θ_{TVP} is the typical population value for an individual with a standardized covariate value, $\theta 2$ is the exponent of the power function. Standardized values of the covariates could be the median in the population of the dataset, or values regarded as standard or normal in the general population. Standard allometric relationships between weight and clearance (exponent=0.75) and weight and volume (exponent=1.0) were included in the covariate-parameter model.

Model evaluation after including body weight effects on CL/F normalized to body weight to the power of 0.75 demonstrated an age-dependent effect on CL/F below 5 years, after which age did not appear to affect CL/F (Figure 3).

Figure 3: Individual Weight (to 0.75 power) -Adjusted CL/F Estimates vs Age



Source: Sponsor's Population PK Study Report, 2011N118856, pg 71

To describe the effect of age on clearance in pediatric patient whose age was less than 2*AG50, the following relationship was used as it was identified as the most appropriate model in the previous analysis:

CLAGE=[1+AMAX*(1-0.5*AGE$_i$/(AG50)]

This relationship was limited to pediatrics with age greater than 2*AG50 (all older pediatrics were assigned CLAGE equal to 1).

Finally, for categorical covariates, the fractional change in the typical parameter value was determined as:
$TVP_i = \theta 1 * \theta 2^{INDi}$
Reviewer's Comments: A relationship of increasing body-weight normalized (to 0.75 power) apparent clearance with decreasing age was unexpected for these pediatrics. Typical allometric scaling combined with effects from hepatic maturation would predict body weight normalized (to the 0.75 power) apparent clearance to further decrease with decreasing age, counter to the above trend. The reviewer performed an independent analysis of the covariate, and the pediatric data supports the sponsor's observation that higher than anticipated clearances (based on allometric scaling of apparent clearance) were observed for pediatrics <3 years of age. A similar relationship was observed for lopinavir/ritonavir, but only for pediatrics <2 months. In the lopinavir/ritonavir analysis it was determined that a reduced bioavailability was the primary contributor in the youngest pediatrics. However, a similar covariate on bioavailability for FPV/RTV could

not be accurately estimated, possibly due to pediatric datasets including multiple formulations with different food effects, dose adjustment during the study, vomiting of administered medications, and adherence. As such, a definitive mechanism for the higher than anticipated apparent clearances could not be determined from the available pediatric data. However, the data is sufficient to provide pediatric dosing recommendations in PI-naïve pediatrics >1 month and PI-experienced pediatrics >6 months.

Population PK Model Results

Final population PK parameter estimates are shown in Table 9. The PK of APV following oral administration of FPV alone or in combination with RTV was adequately described by a 2-compartment model with first order absorption and elimination.

Table 9: Final Population PK Parameter Estimates

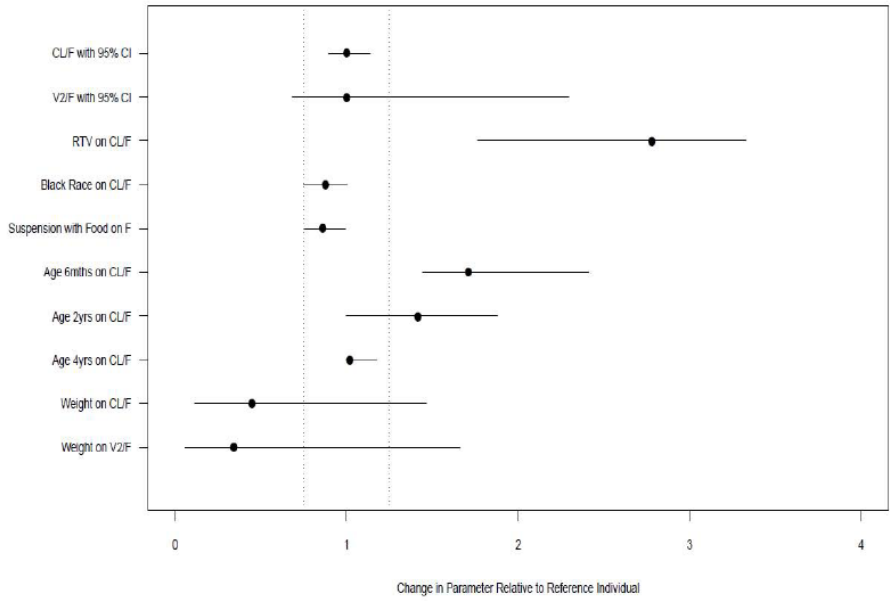
Parameter [Units]	NONMEM Estimate [%RSE]	Bootstrap Estimate[b] Median (95% CI)
CL/F [L/hr] (+ RTV)	26.7 [5.84]	27.0 (23.9, 30.3)
V2/F [L]	134 [27.4]	202 (91.5, 308)
Q/F [L/hr]	74.2 [12.0]	67.4 (47.1, 88.8)
V3/F [L]	8000 (FIXED)	8000 (FIXED)
Ka1 [hr-1]	0.682 [16.3]	1.01 (0.585, 1.77)
CL/F (- RTV)	52.1 [19.6]	60.1 (36.8, 81.7)
Fsus,fed	0.861 [6.21]	0.875 (0.757, 0.996)
CL/F~Age[a]		
AMAX	0.809 [38.3]	1.07 (0.663, 1.59)
AG50 [months]	24.6 [0.052]	14.5 (9.00, 27.0)
CL/F~WT, Q/F~WT	0.75 (FIXED)	0.75 (FIXED)
V2/F~WT, V3/F~WT	1.00 (FIXED)	1.00 (FIXED)
CL/F~Black Race	0.876 [8.42]	0.866 (0.748, 1.00)
Inter-individual Variability (IIV)		
ηCL variance	0.199 [18.2] (CV=44.6%)	0.190 (0.129, 0.268)
ηVc variance	0.252 [61.9] (CV=50.2%)	0.0512 (0, 0.604)
ηQ variance	1.01 [34.9] (CV=100%)	1.03 (0.488, 1.78)
Residual Variability		
σ^2prop	0.255 [8.82] (CV=50.5%)	0.254 (0.206, 0.298)
σ^2add	0.073 [45.1]	0.068 (0.025, 0.166)

c. Typical value of CL/F multiplied by FAGE; where FAGE=1+AMAX*(1-0.5*AGE/AG50)
The reference population for PK parameters is a >4 year, 70 kg, White individual receiving FPV tablets or the oral suspension in the fasted state.
d. Bootstrap analysis was stratified by age group.
Abbreviations: %RSE: percent relative standard error (SE) of the estimate = SE/parameter estimate * 100, CV% = coefficient of variation, CL/F = apparent clearance, V2/F = apparent volume of central compartment, Q/F = apparent inter-compartmental exchange flow rate, V3/F = apparent volume of peripheral compartment, Ka1 = absorption rate constant, Fsusp,fed = fraction of bioavailability of oral suspension when administered with food relative to without food, AMAX = maximal age effect on CL/F (see footer a), AG50 = age at half maximal effect on CL/F (see footer a), WT = weight, CL/F~Age = CL/F x FAGE (see footer a), CL/F~BlackRace = fraction of CL/F for Black subjects relative to subjects of other race.

Source: Sponsor's Population PK Study Report, 2011N118856, pg 6

The effects of covariates on PK parameters, using the point estimate from the original fit and the 95% CI from the bootstrap, are displayed in Figure 4. RTV co-adminsitration had the largest impact on plasma APV CL/F. Co-administration with RTV was estimated to decrease plasma APV CL/F by 49% (95% CI: 18%, 71%), which would lead to an

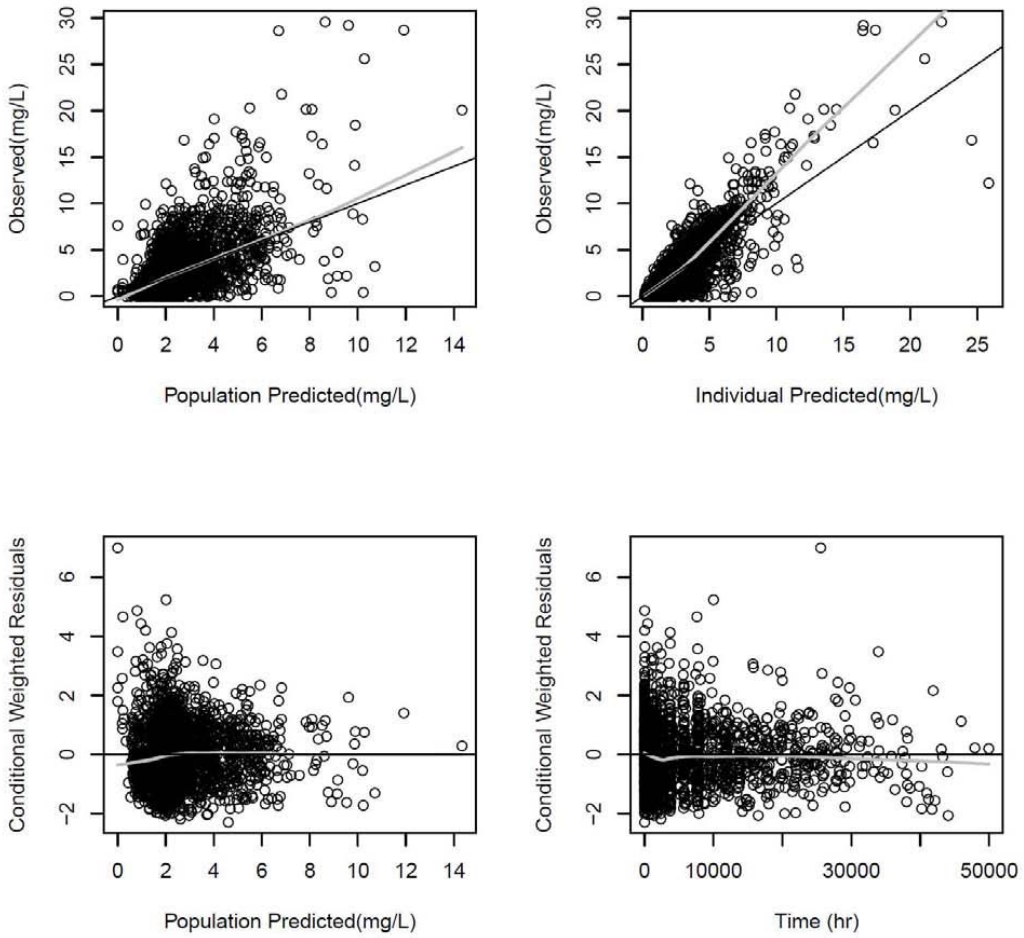
Figure 4: Covariate Effects for the Final Population PK Model



Source: Sponsor's Population PK Study Report, 2011N118856, pg 72

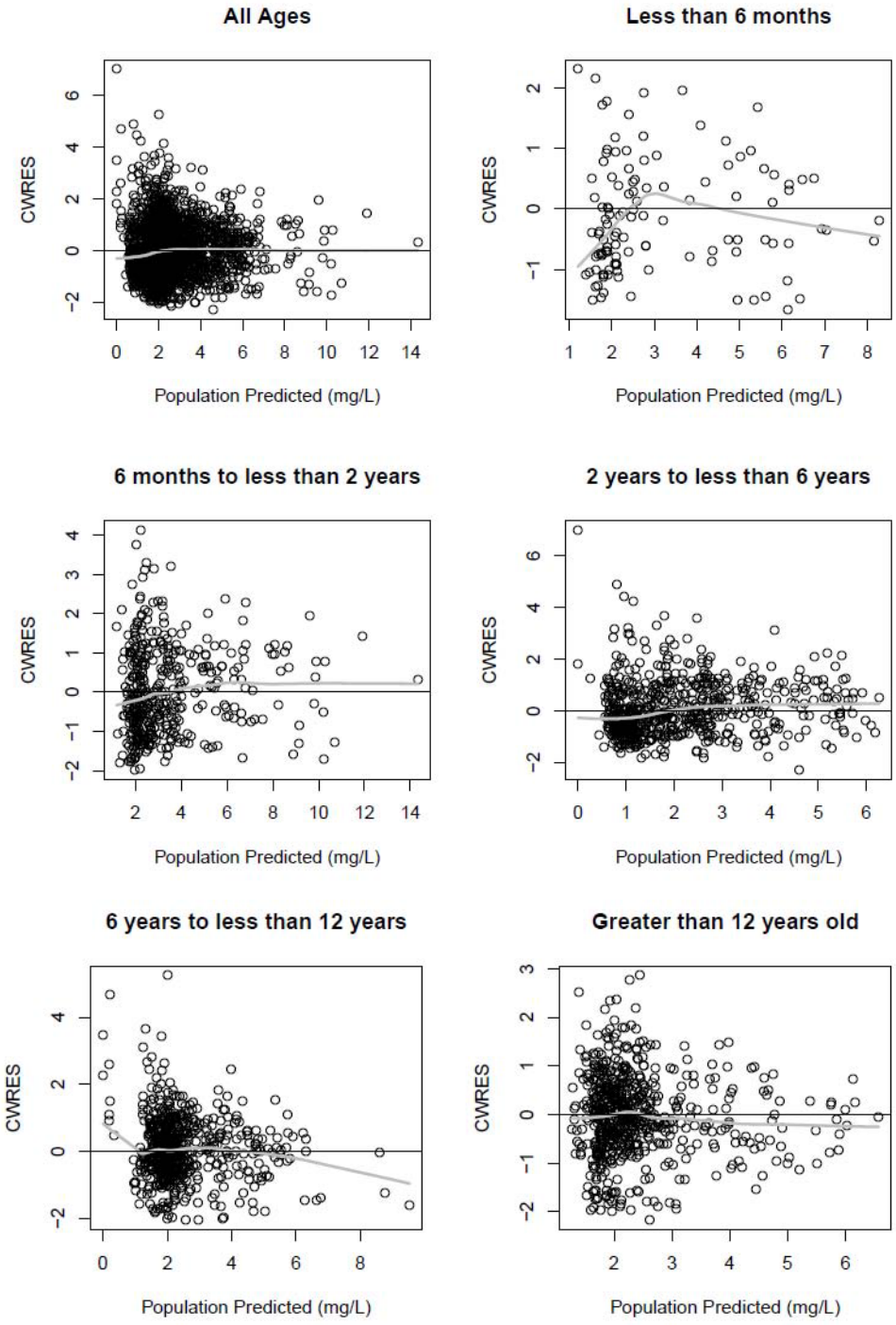
Reviewer's Comments: The diagnostic analyses suggest that the final population PK model is reasonably able to characterize the amprenavir PK profiles in the studied population. The predictive performance analyses suggest that the final population PK model provides acceptable predictive performance of the central tendency and variability of the key amprenavir exposure parameters (Figure 5, Figure 6, and Figure 7). Therefore, the simulation results based on the final population PK model are reasonable. However, the reviewer further evaluated the appropriateness of the estimated AG50 parameter that supports dosing in pediatrics 2-<3 years.

Figure 5: Goodness of fit - observed vs. population and individual predictions (top) and conditional weighted residual versus population predictions and time (bottom) (final model)



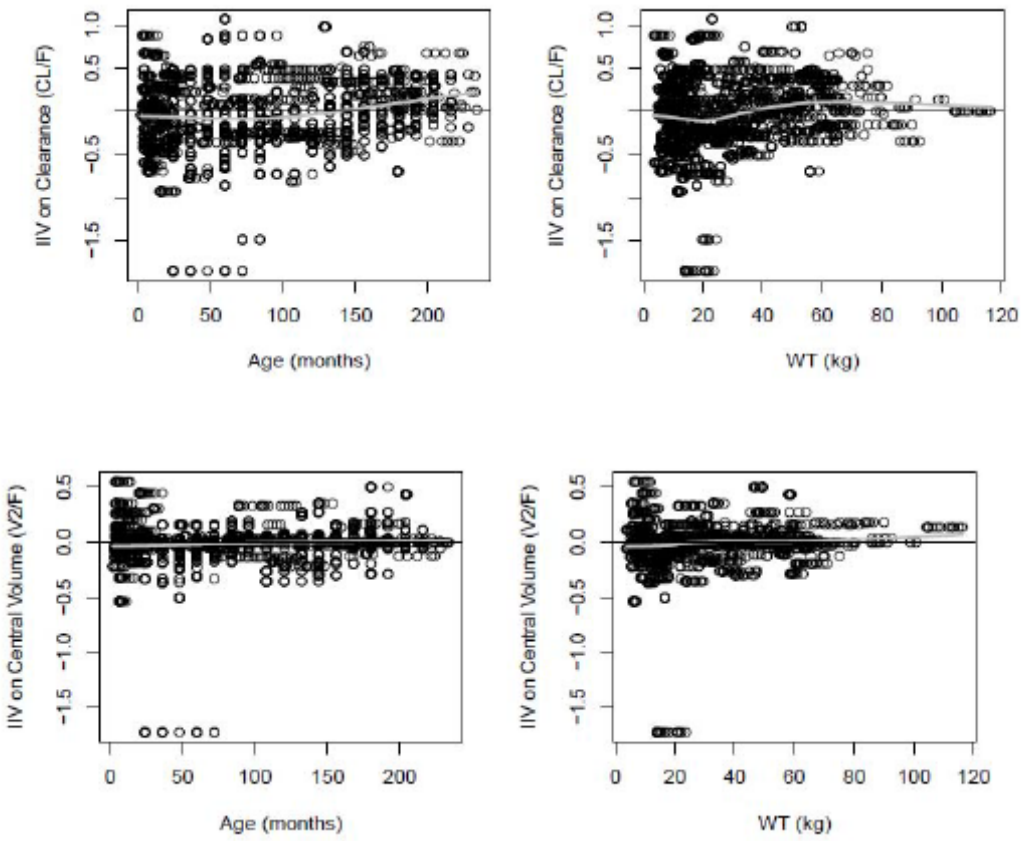
Source: Sponsor's Population PK Study Report, 2011N118856, pg 59

Figure 6: Conditional Weighted Residuals vs Population Predicted Plasma Amprenavir Concentration by Age: Final Model



Source: Sponsor's Population PK Study Report, 2011N118856, pg 60

Figure 7: ETAs vs Continuous Covariates



Source: Sponsor's Population PK Study Report, 2011N118856, pg 67

The sponsor used all available data for evaluating pediatrics pharmacokinetics of amprenavir, including subjects administered fosamprenavir in the absence of ritonavir. Given the influence that the AG50 parameter has on dose selection for pediatrics 2-3 years of age and the divergent estimation and boot strap results for this parameter, the reviewer performed a sensitivity analysis of the sponsor's model by only estimating parameters based on only pediatrics administered FPV/RTV. Results of this analysis are included below in the reviewer's analysis and demonstrate agreement with the sponsor's bootstrap results. In addition, the reviewer was unable to recreate the sponsor's estimation results with the supplied pediatric dataset; however, the estimation was ultimately similar to the sponsor's bootstrap results. This suggest that the parameters from the bootstrap estimates (with an AG50 of 14.5 months) may be more appropriately for selecting pediatric doses, especially for pediatrics <4 years

Pediatric Dose Simulations: Age-Band Dosing

Simulations were performed to determine appropriate pediatric age groups and associated FPV/RTV BID dosage regimens predicted to maintain plasma APV exposure similar to adult exposure.

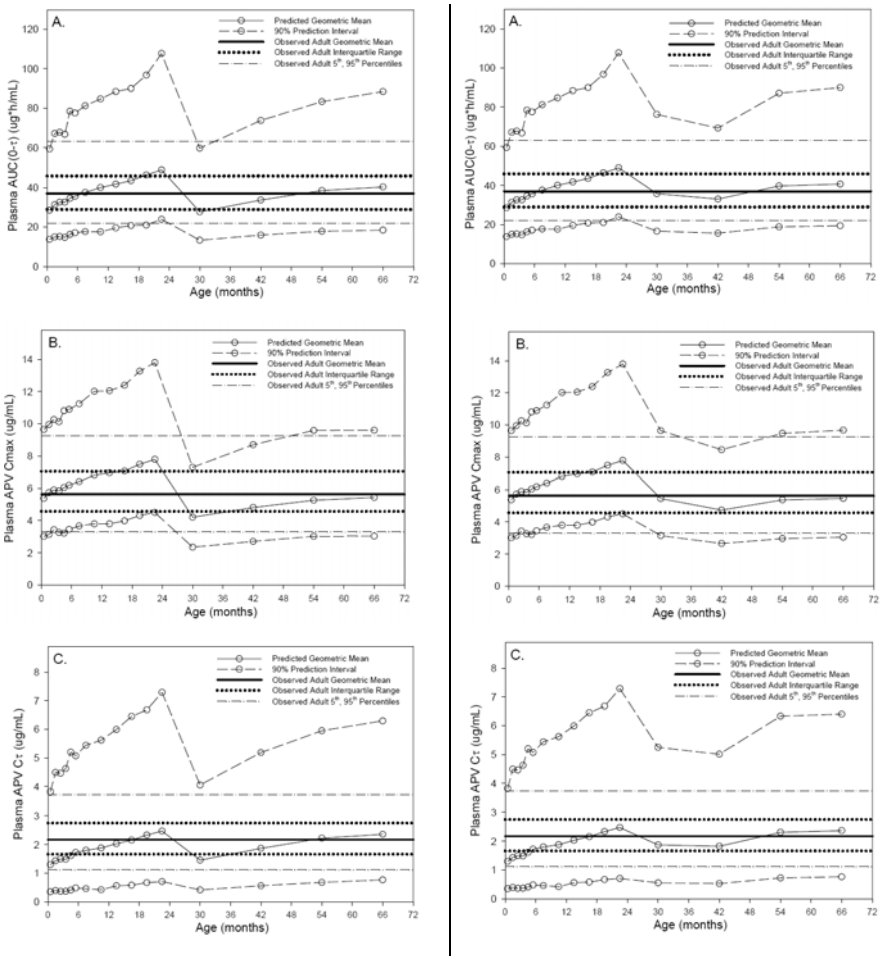
Each age division was represented by 1000 simulated subjects. The age divisions were

1 month for subjects <6 months, 3 months for subjects 6 months to <2 years, and 1 year for subjects ≥2 years. Weights were randomly selected from the interquartile range (25th to 75th percentile) from the Centers for Disease Control and Prevention (CDC) growth charts based on randomly selected age (uniform distribution within each age division) and gender (uniform distribution). Race was approximately evenly distributed between Black and non-Black subjects. Dosing was assumed to always occur in the fed state. Subjects age 12 and older received the tablet formulation while subjects less than 12 received the oral suspension formulation.

Simulated geometric mean (90% prediction interval) plasma APV PK parameters (AUC(0-τ), Cmax and Cτ) for the following age groups and FPV/RTV BID dosage regimens were successful in maintaining plasma APV exposure consistent with observed adult exposure following FPV/RTV 700/100 mg BID:

- 1 to <24 months: 45/7 mg/kg BID
- 2 to <3 years: 30/3 mg/kg BID
- 3 to <6 years: 23/3 mg/kg BID
- 6 to <18 years: 18/3 mg/kg BID (up to maximium dose of 700/100 mg BID)

Figure 8: Simulated Plasma APV AUC(0-tau) (Panel A), Cmax (Panel B), and Ctau (Panel C) for FPV/RTV BID 45/7 mg/kg BID for Pediatric Subjects 4 weeks to <2years (left and right) and 23/3 mg/kg BID for 2 to <6 years (left) or 30/3 mg/kg BID for 2 to <3years, and 23/3 mg/kg BID for 3 to <6 years (right) Compared with Observed Adult Parameters for FPV/RTV 700/100 mg BID.



Source: Sponsor's Population PK Study Report, 2011N118856, pg 32-35

The proportions of pediatric subjects with simulated plasma APV Cmax, AUC(0-τ), and Cτ estimates outside of the 20th to 80th percentiles observed in healthy adults ranged from 43.7% (Cmax in 4 week to <6 month old subjects) to 68.2% (Cτ in 6 month to <2 year old subjects). In general, Cmax exhibited the lowest proportion and Cτ the highest proportion of simulated values outside of the 20th to 80th percentiles window of healthy adults.

Table 10: Proportion (%) of Pediatric Subjects Predicted to Achieve Plasma APV PK Parameters <20th Percentile, 20th-80th Percentile, and >80th Percentile of Adult PK Values for FPV/RTV BID

Pediatric Age Group & FPV/RTV BID Regimen	Cmax Percentile			AUC(0-τ)			Cτ		
	<20th	20-80th	>80th	<20th	20-80th	>80th	<20th	20-80th	>80th
4wk-<6mo 45/7 mg/kg	19.4	55.5	25.1	36.0	45.1	18.9	48.6	32.2	19.2
6mo-<2yr 45/7 mg/kg	8.0	46.1	45.9	17.4	44.1	38.5	32.3	32.0	35.7
2-<3yr 30/3 mg/kg 3 to <6 year 23/3 mg/kg	29.9	53.8	16.3	26.2	46.3	27.5	31.6	35.0	33.4
6-<12y 18/3 mg/kg	43.1	47.9	9.03	31.0	46.1	22.9	32.6	36.7	30.7
12-<18y 700/100 mg	49.2	42.5	8.3	31.8	46.1	22.1	32.9	37.6	29.5

20th & 80th percentile values for adults receiving FPV/RTV 700/100 mg BID: Cmax: 4.34 μg/mL, 7.38 μg/mL, AUC(0-τ): 27.6 μg.h/mL, 49.0 μg.h/mL, Cτ: 1.59 μg/mL, 2.89 μg/mL

Source: Sponsor's Population PK Study Report, 2011N118856, pg 36

The distribution of simulated plasma APV Cmax, AUC(0-τ), and Cτ values for pediatric subjects was generally consistent with the distribution of observed values for adults; although it could be seen that there was more variability in the pediatric data. Deviations between simulated plasma APV Cmax, AUC(0-τ), and Cτ values for pediatric subjects and observed values for adults were smallest near the median and largest near the highest and lowest percentiles.

Table 11: Percent Deviation of APV PK Parameter Percentiles for Simulated Pediatric FPV/RTV BID Regimens versus Observed Values in Adults Receiving FPV/RTV 700/100 mg BID

PK Parameter	Percentile	Adults FPV/RTV 700/100 BID	4weeks to <6months 45/7mg/kg BID		6months to <2years 45/7mg/kg BID		2 to <3 years 30/3mg/kg BID 3 to <6 years 23/3mg/kg BID		6 to <12 years 18/3mg/kg BID		12 to <18 years 700/100mg BID	
			Value	% deviation	Value	% deviation	Value	% deviation	Value	% deviation	Value	% deviation
AUC(0-τ) (μg•h/mL)	10	24.8	17.8	-28	23.3	-6.0	20.3	-18	19.2	-23	18.6	-25
	20	27.6	21.7	-21	28.8	4.3	25.0	-9.4	23.5	-15	23.2	-16
	50	37.4	32.8	-12	43.0	15	37.6	0.5	34.8	-7.0	34.6	-7.5
	80	49.0	48.1	-1.8	63.4	29	55.1	12	51.0	4.1	50.6	3.3
	90	56.9	58.5	2.8	78.0	37	66.9	18	62.5	10	62.9	11
Cmax (μg/mL)	10	3.84	3.73	-2.9	4.52	18	3.35	-13	2.95	-23	2.75	-28
	20	4.34	4.38	0.9	5.28	22	3.92	-9.7	3.41	-21	3.23	-26
	50	5.67	5.87	3.5	7.11	25	5.28	-6.9	4.62	-19	4.37	-23
	80	7.38	7.81	5.8	9.46	28	7.05	-4.5	6.16	-17	5.99	-19
	90	8.77	9.05	3.2	11.1	27	8.29	-5.5	7.24	-17	7.06	-19
Cτ (μg/mL)	10	1.36	0.548	-60	0.792	-42	0.851	-37	0.856	-37	0.857	-37
	20	1.59	0.817	-49	1.18	-26	1.20	-25	1.22	-23	1.23	-23
	50	2.21	1.63	-26	2.25	1.8	2.21	0	2.12	-4.1	2.12	-4.1
	80	2.89	2.84	-1.7	3.89	35	3.67	27	3.47	20	3.45	19
	90	3.40	3.73	9.7	5.08	49	4.66	37	4.43	30	4.42	30

Source: Sponsor's Population PK Study Report, 2011N118856, pg 41

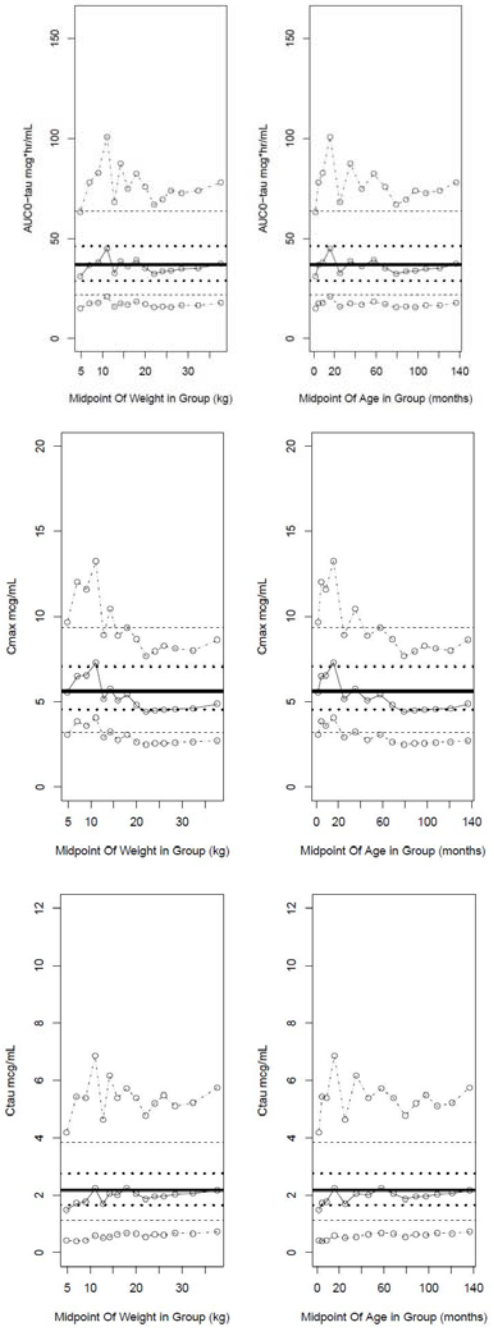
Pediatric Dose Simulations: Weight-Band Dosing

In addition to the above analyses based on FPV/RTV age-bands, the sponsor was requested to provide dosing recommendations and simulation results using weight-bands. The weight-bands proposed by the sponsor are listed below:

Simulations for the above weight-bands were performed similar to the methods discussed above for the age-bands. Simulated geometric mean (90% prediction interval) plasma APV PK parameters ($AUC_{(0-\tau)}$, C_{max} and C_{τ}) for the above weight-bands and FPV/RTV BID dosage regimens achieved plasma APV exposure consistent with that observed from the age-bands.

Figure 9: Simulated Plasma APV $AUC_{(0\text{-}tau)}$ (top), C_{max} (middle), and C_{tau} (bottom) for (b) (4) FPV/RTV Dosage Regimens:

- **45/7 mg/kg BID <12kg or 4 weeks to <2years**
- **30/3 mg/kg BID 12-<15kg or 2 to <3years**
- **23/3 mg/kg BID 15-<20kg or 3 to <6 years**
- **18/3mg/kg BID 20-<40kg or ≥6 years**



Source: Sponsor's Response to FDA Clinical Requests for Additional Information Dated 20 January 2012, pg 9-11

Reviewer's Comments: The sponsor was requested to perform an age-band versus weight-band dosing comparison during the review process. While age-bands were evaluated in the pediatric studies, it is more conventional to employ weight-band dosing for pediatrics (see labels for Kaletra®[1], darunavir[2], and atazanavir[3]). The sponsor's proposed weight-band dosing is analogous to the age-band dosing based on the CDC growth charts and attains similar exposures across pediatric groups (b) (4) *. As such, the final pediatric dosing recommendations are to recommend the weight-band dosing recommendations.*

1. *Kaletra label. In. Food and Drug Administration, Center for Drug Evaluation and Research: (http://www.accessdata.fda.gov/drugsatfdadocs/label/2012/021226s035lbl.pdf)*
2. *Darunavir label. In. Food and Drug Administration, Center for Drug Evaluation and Research: (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021976s022lbl.pdf)*
3. *Atazanavir label. In. Food and Drug Administration, Center for Drug Evaluation and Research: (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021567s028lbl.pdf)*

4 REVIEWER'S ANALYSIS

4.1 Introduction

An independent pharmacometric analysis is presented that evaluates the conclusions made by the sponsor regarding the AG50 parameter in the population PK model. This parameter, which informs dosing (b) (4) in pediatric 2-<3 years of age, decreased during bootstrap evaluation of the sponsor's final model. The reviewer aims to determine if the (b) (4) parameter value (24.6 months) or the bootstrap value (14.5 months) is more appropriate for guiding pediatric dosing recommendations.

4.2 Objectives

Analysis objectives are:

1. Perform a sensitivity analysis on key parameters (AG50) from the sponsor's model describing age-effects on apparent clearance

4.3 Methods

4.3.1 Data Sets

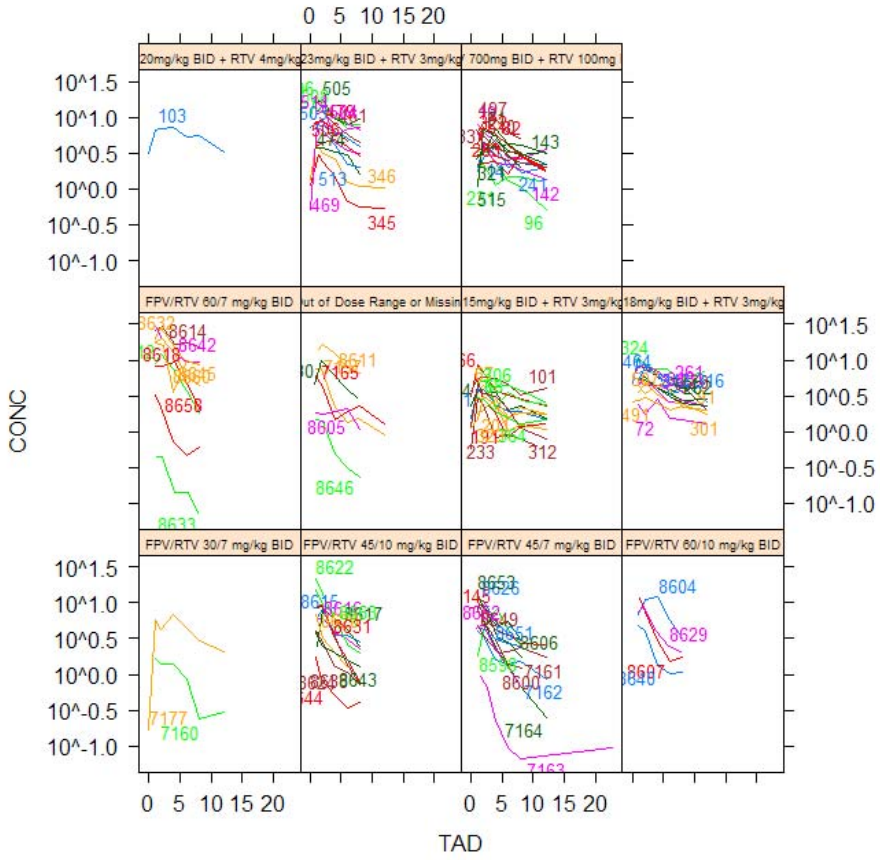
Data sets used are summarized in Table 12.

Table 12. Analysis Data Sets

Study Number	Name	Link to EDR
APV20002	pkcnc.xpt	\\Cdsesub1\evsprod\NDA021548\0076\m5\datasets\apv20002\analysis\datasets
APV29005	pkcnc.xpt	\\Cdsesub1\evsprod\NDA021548\0076\m5\datasets\apv29005\analysis\datasets
APV20003	pkcnc.xpt	\\Cdsesub1\evsprod\NDA021548\0076\m5\datasets\apv20003\analysis\datasets
Population PK	apv-nm.xpt	\\Cdsesub1\evsprod\NDA021548\0076\m5\datasets\2011n118856\analysis\data sets

Demographics and data for the original population PK analysis are summarized above in Table 8. Concentration versus time profiles for pediatrics from APV20002 and APV29005 are shown below in Figure 10, grouped according to dosing regimen (BID only).

Figure 10: APV PK Time Course from Intensive Sampling for Various FPV/RTV Dosing Regimens



4.3.2 Software

R (Version 2.10.0) was used to generate all plots. NONMEM version 7.2 (Icon) was used to evaluate the population PK model.

4.3.3 Models

The sponsor's model was revised using the following three approaches to determine the sensitivity of key model parameters to the data available:

- Rerun the submitted sponsor's model due to divergent results between the final model parameter estimates and bootstrap results (model 1)
- Estimate parameters using only those pediatrics administered FPV/RTV (model 2)

The motivation behind the first analysis was to verify the sponsor's original analysis. The second analysis aimed to identify if parameter estimates would differ using only those patients administered FPV/RTV as the sponsor only included the impact of RTV on apparent clearance in their original model (alternatively, RTV could impact bioavailability, which would be observed as a change on all model parameters). The data set for this analysis included 192 pediatrics (age: 2 months to <18 years; body weight: 4 to 104 kg) and 2113 PK samples.

4.3.4 Pediatric Dosing Simulation Plan

Simulations were performed using completed population pharmacokinetic models from the above scenarios to evaluate the proposed FPV/RTV doses to achieve target adult exposures receiving 700/100 mg FPV/RTV BID (AUC ~ 37 ug•hr/mL, C_{max} ~ 5.6 ug/mL, C_{τ} ~ 2.2 ug/mL for adults). Mean, 5th, and 95th percentile body weights for pediatrics were obtained using CDC growth chart data (http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm#Clin%201). Simulations were performed using mean estimated parameters and median, 5th, and 95th percentile weights from the age~body weight relationships. AUC in pediatrics was calculated using the sponsor's (b) (4) age- and weight-band dosing nomograms, the (b) (4) age-band dosing nomogram, and the reviewer's adjusted weight-band dosing nomogram. The final dosing regimen was selected based on comparable simulated APV exposures in pediatrics and AUC in adults

4.4 Results

Population PK Modeling Results

Diagnostic plots for the rerun of the sponsor's model with the full dataset (model 1) and only those pediatrics receiving FPV/RTV (model 2) is shown in Figure 11. The diagnostic analyses suggest that the final population PK model is reasonably able to characterize the amprenavir PK profiles in the studied population, though there is a subset of amprenavir observations over-predicted by the model. Given that a majority of these observations are for amprenavir concentrations <0.1 µg/mL, this over prediction is likely due to drug adherence.

Inter-individual variability plots were also evaluated for apparent clearance versus the continuous covariates age and weight for both models (Figure 12). Both plots

demonstrate adequate performance from the model and no trend in estimated inter-individual variability for either covariate with either model.

Figure 11: Goodness of fit - observed vs. individual predictions for model 1 (left) and model 2 (right). Observations are grouped according to age category (category 1: at least 4 weeks to <6 months; category 2: 6 months to <2 years; category 3: 2-<3 years; and category 4: 3-<6 years)

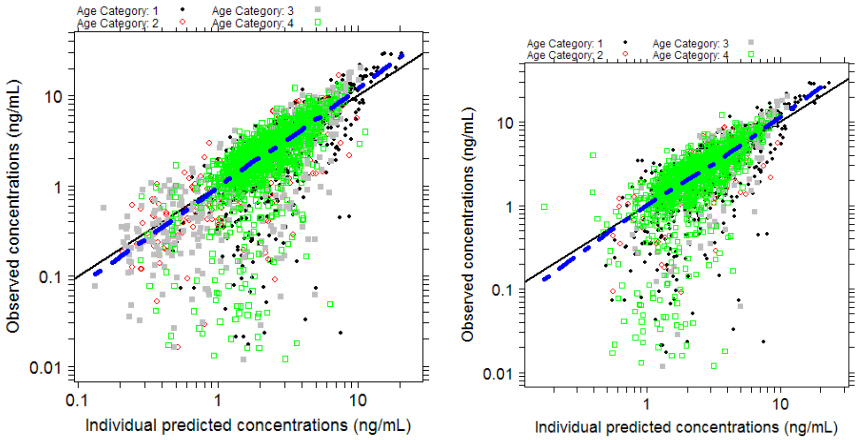
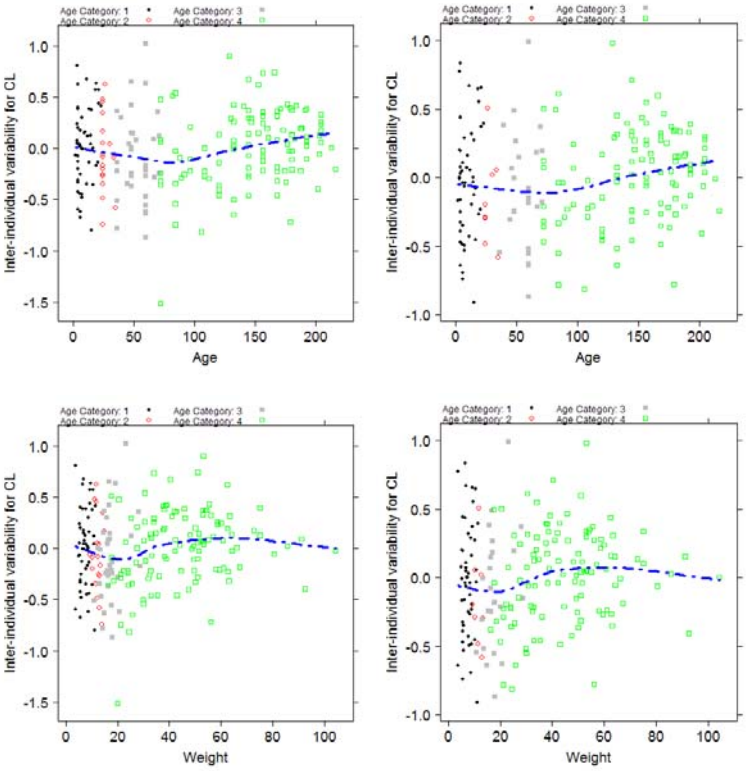


Figure 12: Inter-individual variability plots for apparent clearance for age (top) and body weight (bottom) for model 1 (left) and model 2 (right). Estimates are grouped according to age category (category 1: at least 4 weeks to <6 months; category 2: 6 months to <2 years; category 3: 2-<3 years; and category 4: 3-<6 years)



Final model parameters based on the pediatric dataset is shown below in Table 13. In addition, the parameter estimates from the sponsor's final model evaluation and bootstrap analysis are included for comparison. The reviewer's evaluation of the sponsor's model was not able to recreate the results; however, the results are in agreement with the sponsor's bootstrap results, suggesting that the bootstrap parameter values may better represent pediatrics administered FPV/RTV. A sensitivity analysis was also performed, removing PK samples where patients were not administered FPV with RTV to determine if this data was influencing parameter estimates. As shown in Table 13, the PK parameter estimates did not substantially change following removal of data points where RTV was not co-administered.

Table 13: NONMEM Parameter Estimates from the Sponsor's Final Model, Bootstrap Analysis, Rerun of the Sponsor's Model, and Sensitivity Analysis Using Only FPV/RTV Data

	Sponsor's Final Model	Sponsor's Bootstrap Results	Reviewer's Rerun of Final Model	Reviewer's Results - Removing RTV- Peds
Fixed-Effects				
CL/F + RTV (L/hr)	26.7 [5.8]	27 (24; 30)	27.6 [6]	28 [5.5]
V2/F (L)	134 [27]	202 (92; 308)	210 [19]	106 [26]
Q/F (L/hr)	74.2 [12]	67 (47; 89)	69.7 [12]	72.5 [14]
V3/F (L)	8000 (FIXED)	8000 (FIXED)	8000 (FIXED)	8000 (FIXED)
Ka1 (hr-1)	0.68 [16]	1.01 (0.59; 1.77)	1.01 [21]	0.50 [19]
CL/F (- RTV)	52 [20]	60 (37; 82)	65.8 [12]	-
Fsus, fed	0.86 [6]	0.88 (0.76; 1.0)	0.89 [6]	0.95 [6]
CL/F -Age				
AMAX	0.81 [38]	1.07 (0.66; 1.59)	0.94 [21]	1.04 [21]
AG50	24.6 [0.05]	14.5 (9; 27)	13.5 [15]	16.5 [0.03]
CL/F~WT, Q/F~WT	0.75 (FIXED)	0.75 (FIXED)	0.75 (FIXED)	0.75 (FIXED)
V2/F~WT, V3/F~WT	1 (FIXED)	1 (FIXED)	1 (FIXED)	1 (FIXED)
CL/F -Black Race	0.88 [8]	0.87 (0.75; 1.00)	0.89 [7]	0.87 [7]
Inter-Individual Variability				
CL	45 [18]	44	41 [8]	41 [7]
V2	50 [62]	23	30 [32]	40 [25]
Q/F (L/hr)	100 [35]	101	91 [17]	85 [14]
Residual Variability				
Prop	0.50 [9]	0.5	0.5 [5]	0.42 [6]
Add	27 [45]	26	26 [28]	61 [14]

Combined with the similarity between the rerun of the sponsor's analysis (model 1) and the sponsor's bootstrap results, model 1 was selected as an adequate description of the population for simulating pediatric exposures.

Pediatric Simulation Results

Using model 1 above, simulations of pediatric exposures for the origin pediatric age-bands were performed for the following scenarios for $AUC_{(0-\tau)}$, C_{max}, and C_{τ}:

Scenario 1: 45/7 mg/kg FPV/RTV BID for pediatrics at least 4 weeks to 2 years
23/3 mg/kg FPV/RTV BID for pediatrics at 2 years to <6 years

Scenario 2: 45/7 mg/kg FPV/RTV BID for pediatrics at least 4 weeks to 2 years
30/3 mg/kg FPV/RTV BID for pediatrics at 2 years to <3 years
23/3 mg/kg FPV/RTV BID for pediatrics at 3 years to <6 years

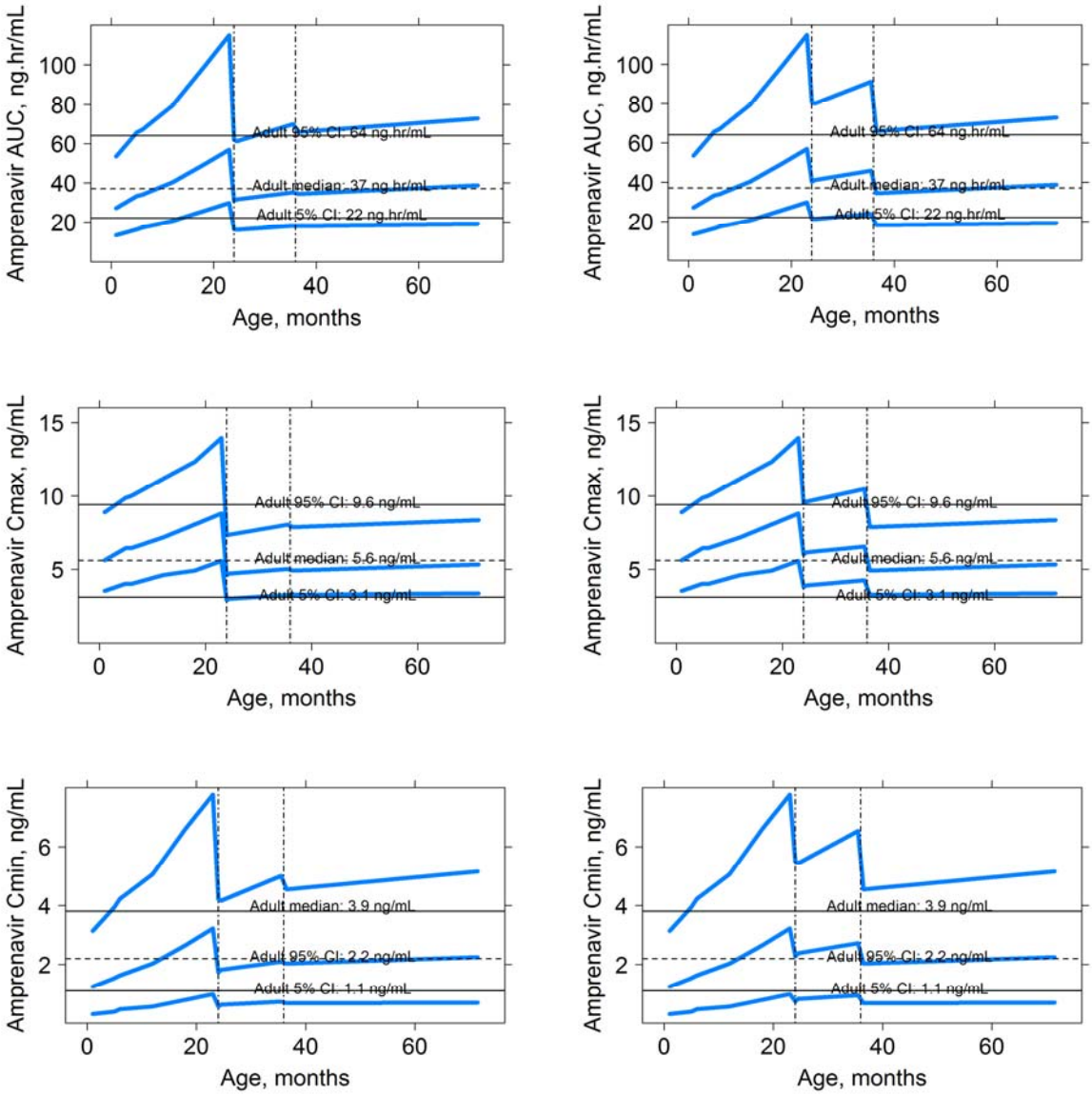
Scenario 3: 45/7 mg/kg FPV/RTV BID for pediatrics <12 kg
30/3 mg/kg FPV/RTV BID for pediatrics 12 - <15 kg
23/3 mg/kg FPV/RTV BID for pediatrics 15 - <20 kg

Scenario 4: 45/7 mg/kg FPV/RTV BID for pediatrics <11 kg
30/3 mg/kg FPV/RTV BID for pediatrics 11-<15 kg
23/3 mg/kg FPV/RTV BID for pediatrics 15-<20 kg

Scenario 5: 60/7 mg/kg FPV/RTV BID for pediatrics <8 kg
45/7 mg/kg FPV/RTV BID for pediatrics 8-<12 kg
30/3 mg/kg FPV/RTV BID for pediatrics 12 - <15 kg
23/3 mg/kg FPV/RTV BID for pediatrics 15 - <20 kg

Scenario 1 includes pediatric doses studied during APV20002 and APV29005. Scenario 2 is the sponsor's [redacted] (b) (4) age-band dosing based on the study and modeling and simulation results to adjust dosing for the age-effect on apparent clearance. These two scenarios are compared side-by-side below.

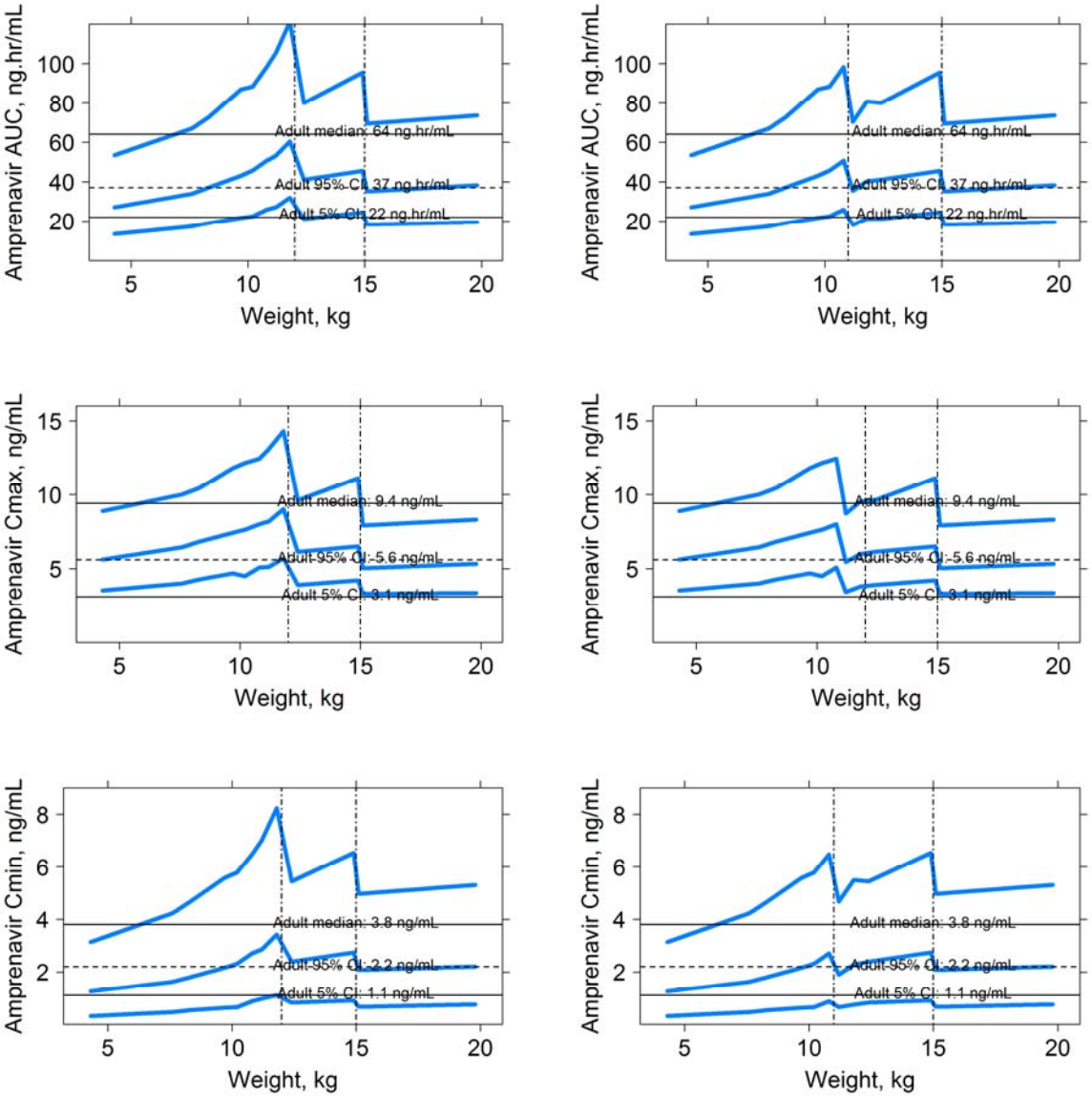
Figure 13: Simulated (median, 5th, and 95th percentile) Plasma APV $AUC_{(0\text{-}tau)}$ (top), C_{max} (middle), and C_{tau} (bottom) for Scenario 1 (left) and Scenario 2 (right) Compared with Observed Adult Parameters for FPV/RTV 700/100 mg BID (median, 5th, and 95th percentile).



Using the rerun of the sponsor's model, the necessity of the separate dosing for pediatrics 2-<3 years is not as apparent as the exposures in pediatrics 2-<3 years is only slightly below the median adult exposures (Figure 13). Increasing the dose in this group to 30/3 mg/kg (right) increases all three exposure metrics above the adult median, but the results of this modeling and simulation analysis also suggests that 30/3 mg/kg may be appropriate in pediatrics 18-<24 months.

This observation was further evaluated in the context of two sets of weight-band based dosing recommendations. Scenario 3 includes the [redacted] (b) (4) weight-band dosing based on the Agency's request on January 11. Scenario 4 includes the final pediatric dosing recommendations [redacted] (b) (4) (Figure 14).

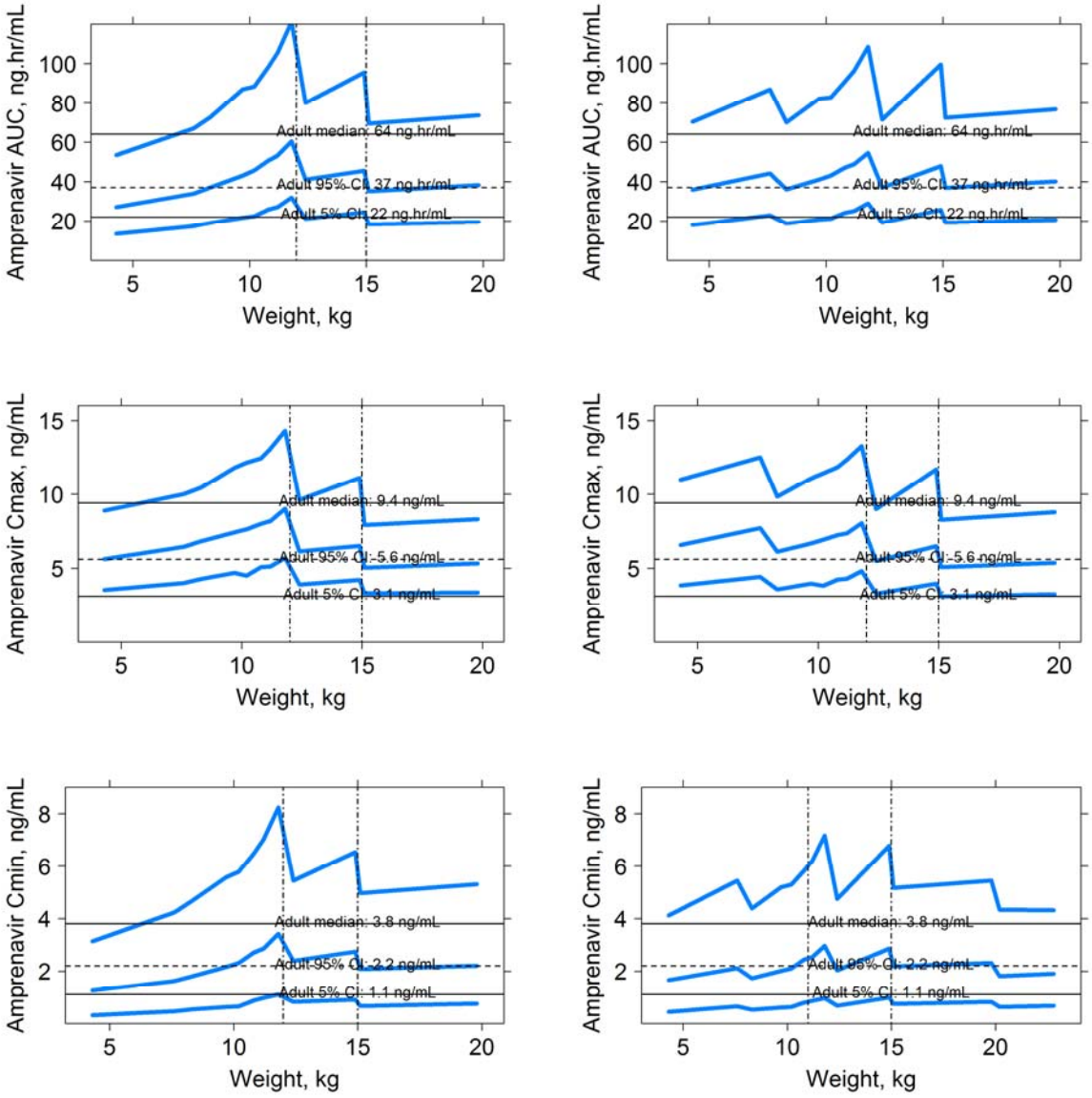
Figure 14: Simulated (median, 5th, and 95th percentile) Plasma APV $AUC_{(0\text{-}tau)}$ (top), C_{max} (middle), and C_{tau} (bottom) for Scenario 3 (left) and Scenario 4 (right) Compared with Observed Adult Parameters for FPV/RTV 700/100 mg BID (median, 5th, and 95th percentile).



Results from Scenario 3 demonstrate reasonable agreement with observed adult exposures for $AUC_{(0\text{-}\tau)}$, C_{max}, and C_{τ}. However, similar to the age-band results, the simulation results indicate that the 30/3 mg/kg dosing recommendation could be extended to weights lower than 12 kg. This was investigated in Scenario 4 with pediatrics 11-<15 kg receiving 30/3 mg/kg. These simulation results are shown above (right) and

demonstrate that the dosing [redacted] (b) (4) from Scenario 4 are suitable for use in pediatrics 8-<20 kg.

Figure 15: Simulated (median, 5th, and 95th percentile) Plasma APV $AUC_{(0\text{-}tau)}$ (top), C_{max} (middle), and C_{tau} (bottom) for Scenario 3 (left) and Scenario 5 (right) Compared with Observed Adult Parameters for FPV/RTV 700/100 mg BID (median, 5th, and 95th percentile).



A final note is the appropriateness of the pediatrics dosing recommendations for pediatrics <8 kg. The [redacted] (b) (4) dosing recommendations are not able to achieve adult C_τ for pediatrics <8 kg, with predicted median pediatric values nearing the adult 5th percentile for pediatrics ~4 kg (Figure 15). Increasing the dose in these pediatrics to 60 mg/kg achieves similar AUC in these pediatrics to that observed in adults with an increase in the C_{max}; however, the C_τ for the entire pediatric remains below the median adult C_τ. In addition, given the lower observed C_τ in pediatrics <6 months than the model

prediction, 2-fold higher C_{max} in a subset of pediatrics <6 months administered 60/10 mg/kg BID, and potential contribution of CYP3A4 maturation in pediatrics 1-3 months, a dose increase to 60/7 mg/kg BID in pediatrics <6 months is not recommended.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Run217 mod	Sponsor's final model	Fosamprenavir_NDA21548_JAF\PPK Analyses\Sponsor Model
Run1217 mod	Final model with RTV-data points removed	Fosamprenavir_NDA21548_JAF\PPK Analyses\Final Model
Pediatric_Dose_Datasets_for_FPV_simulation_RUN217.R	Pediatric simulation plots for run217	Fosamprenavir_NDA21548_JAF\PPK Analyses\Simulations\RUN217
Pediatric_Dose_Datasets_for_FPV_simulation_RUN1217.R	Pediatric simulation plots for run1217	Fosamprenavir_NDA21548_JAF\PPK Analyses\Simulations\RUN1217
Pediatric_Dose_Datasets_for_FPV_simulation.R	Construct pediatric simulation dataset	Fosamprenavir_NDA21548_JAF\PPK Analyses
Treatment_arm_data.R	Summary population PK information for APV20002 and APV290005	Fosamprenavir_NDA21548_JAF\PPK Analyses

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIONNA J GREEN
04/04/2012

JEFFRY FLORIAN
04/04/2012

YANING WANG
04/04/2012

SHIRLEY K SEO
04/04/2012