CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-116

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-116	Submission Date: December 13, 2006
Brand Name	LEXIVA
Generic Name	FOSAMPRENAVIR
Reviewer	Vikram Arya, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	DAVP
Sponsor	Glaxo Smith Kline
Relevant IND(s)	IND 58, 627
Submission Type; Code	505 (b) (1), 1P
Formulation; Strength(s)	Oral Suspension, 50 mg/mL
Dosing regimen	**Treatment Naïve Subjects:**
(Approved in Adults)	1400 mg BID
	1400 mg QD, co-administered 200 mg ritonavir QD,
	700 mg BID, co-administered with 100 mg ritonavir BID.
	Treatment experienced subjects:
	700 mg, co-administered with 100 mg ritonavir BID.
Indication	Treatment of HIV-1 infection

Table of Contents

1. Executive Summary

Fosamprenavir (Lexiva, fosamprenavir calcium, FPV) is the phosphate ester pro-drug of the HIV protease inhibitor, amprenavir (Agenerase [AGN], APV). FPV 700 mg tablets are approved for use alone (without ritonavir), and in combination with low-dose ritonavir (RTV), for the treatment of adults with HIV-1 infection. Currently, **there is no labeling recommendation for administration of FPV, with or without ritonavir, in HIV infected subjects < 18 years of age.**

The amprenavir capsules (50 mg) and oral solution (15 mg/mL) are marketed in the United States, for treatment of HIV-1 infection in patients 4 years of age and older. However, due to the risk of toxicity from a large quantity of propylene glycol, amprenavir oral solution is contraindicated in infants and children below 4 years of age.

The applicant has developed the FPV oral suspension which contains lower concentrations of propylene glycol [ ] compared to 550 mg/mL in amprenavir oral solution). In addition, the FPV oral suspension contains no Vitamin E (compared to 46 IU/mL for AGN) and is more concentrated (50 mg/mL compared with 15 mg/mL), thereby reducing the dosing volumes. A liquid formulation will be useful for patients who are unable or unwilling to take the tablet formulation, and for patients who must take lower doses (e.g. subjects with hepatic impairment and pediatric patients) than can be achieved with the currently marketed 700 mg tablet. b(4)

To support the approval of the suspension formulation, the applicant conducted two relative bioavailability studies (**APV10016** and **APV10024**) in order to demonstrate the similarity in systemic exposures after administration of the suspension and tablet formulations.

The applicant conducted a clinical study (**APV10017**) to determine the dosing recommendations of ritonavir boosted fosamprenavir in subjects with mild and moderate hepatic impairment. The dosing recommendations of un-boosted fosamprenavir for severe hepatic impairment have been proposed based on the previous amprenavir pharmacokinetic and safety data.

The applicant conducted two pivotal clinical studies (**APV29005** and **20003**) to determine the dosing recommendations of un-boosted and ritonavir-boosted fosamprenavir in pediatric subjects, 2-18 years old. The applicant developed a pharmacokinetic model based the data collected in the two studies. This model was used to simulate the exposures at the various proposed doses/dosing regimens in pediatric subjects.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in this NDA and the information provided supports the following conclusions:

- The Clinical Pharmacology and Biopharmaceutics Information pertaining to similarity in exposures between the suspension and tablet formulation is acceptable. The information provided supports the approval of the suspension.
- The Clinical Pharmacology and Biopharmaceutics Information provided to support the dosing recommendations for subjects with different degrees of hepatic impairment is acceptable. The information provided supports the following dosing recommendations:
    - **Mild Hepatic Impairment** (Treatment Naïve or Treatment Experienced Subjects with Child-Pugh Score 5-6): **FPV 700 mg BID + RTV 100 mg QD.**
    - **Moderate Hepatic Impairment** (Treatment Naïve or Treatment Experienced Subjects with Child-Pugh Score 7-9): **FPV 450 mg BID + RTV 100 mg QD.**
    - **Severe Hepatic Impairment** (Treatment Naïve Subjects with Child-Pugh Score 10-12): **FPV 350 mg BID.**
- Due to the lack of safety data, some of the dosing regimens proposed by the applicant are not acceptable. Therefore, only those dosing regimens that provided systemic exposures similar to adult systemic exposures and have adequate safety will be approved. The following dosing regimens will be approved:
    - **Therapy Naïve Subjects:**
        - 2-5 years old: FPV 30 mg/kg BID
        - ≥ 6 years old: FPV 30 mg/kg BID (based on previously approved amprenavir pediatric dosage).
    - **Therapy Naïve or Experienced Subjects:**
        - ≥ 6 years old: FPV/RTV 18/3 mg/kg BID

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Fosamprenavir (FPV), a pro-drug of amprenavir (APV), is a protease inhibitor (PI) approved for the treatment of HIV-1 infection. Three dosing regimens of fosamprenavir are currently approved:

Treatment Naïve Adult Patients:

1400 mg BID
1400 mg QD + 200 mg RTV QD
700 mg BID + 100 mg RTV BID

Treatment Experienced Adult Patients:

700 mg BID + 100 mg RTV BID

b(4)

As the regimens outlined above have shown efficacy in well controlled clinical trials in the adult populations, the exposures observed in adults at these approved dosing regimens were used as target exposures in the pivotal pediatric studies (to meet regulatory objective # 2 below). Further, the b.i.d. dosing in pediatric subjects was selected to match the exposures observed after a b.i.d. dosing regimen (700/100 mg BID) in adults. Similarly, the un-boosted dosing in pediatric subjects was selected to provide exposures similar to the exposures observed with the un-boosted dosing regimen (1400 mg BID) in adults.

The studies conducted by the applicant were designed to meet the following three regulatory objectives:

1. To seek approval of the FPV 50 mg/mL oral suspension formulation by demonstrating similarity in exposures (C_{max} and AUC) after oral administration of the suspension formulation and the tablet formulation.
2. To seek approval of un-boosted (without low-dose ritonavir) and boosted (with low-dose ritonavir) FPV containing regimens in HIV-infected pediatric patients 2-18 years of age.
3. To seek approval of the dosing recommendations of FPV oral suspension and tablets in HIV infected subjects with hepatic impairment.

Objective # 1 (Approval of Oral Suspension)

In order to support the first objective, the applicant conducted two relative bioavailability studies (**APV10016** and **APV10024**).

Study **APV10016** was a single dose, open-label, crossover study to assess the relative bioavailability of the FPV oral suspension and tablet formulations and the effect of food on the bioavailability of these formulations in healthy adult subjects.

Table 1 shows the pharmacokinetic parameters observed after treatment A (tablet administered under fasting conditions) and treatment C (suspension administered under fasting conditions).

Table 1: Statistical analysis of the pharmacokinetic parameters of APV observed after treatment A (tablet administered under fasting conditions) and treatment C (suspension administered under fasting conditions).

Plasma APV PK Parameter	Geometric LS Mean		Ratio (90% CI) C/A
	Tablet Fasted (Treatment A)	Suspension Fasted (Treatment C)	
AUC_{∞} (µg.h/mL)	16.52	15.86	0.960 (0.843-1.093)
AUC_{last} (µg.h/mL)	16.14	15.48	0.959 (0.843-1.092)
C_{max} (µg/mL)	4.03	4.62	1.145 (1.011-1.297)
t_{max} (h)	1.83	1.16	0.633 (0.420-0.847)
$t_{½}$ (h)	4.02	4.25	1.055 (0.909-1.225)
Treatment A: Two GW433908 oral film-coated 700mg tablets administered fasted. Treatment C: 28mL of 50mg/mL GW433908 oral suspension administered fasted.			

a. t_{max} is presented as Geometric LS mean and ratio of the Geometric LS means.

The major findings from study **APV10016** were as follows (for details regarding the study design, please refer to the individual study report):

1) Under fasted conditions, the suspension and film coated tablet were equivalent with respect to $AUC_{0-\infty}$. APV C_{max} after administration of suspension formulation was 14.5 % higher as compared to tablets.
2) Administration of oral tablet with high-fat breakfast resulted in equivalent plasma AUC and C_{max} as compared to exposures under fasted conditions.
3) Administration of suspension formulation with high-fat breakfast decreased the mean APV AUC and C_{max} values by 28 % and 46 % as compared to exposures under fasted conditions.

Study **APV10024** was an open-label, randomized, crossover study to assess the relative bioavailability of the fosamprenavir 50 mg/mL oral suspension and tablet formulations following administration of single 1400 mg doses and following administration of 1400 mg BID for 10 days in healthy adult subjects.

Table 2 shows the summary of pharmacokinetic results {geometric mean (95 % CI)[% CV]} of APV after the various treatments.

Table 2: Summary of pharmacokinetic results {geometric mean (95 % CI)[% CV of APV after treatment A, B, C, and D}.

Plasma APV PK Parameter	Single Dose Part N=75		Repeat Dose Part N=71	
	Treatment A	Treatment B	Treatment C	Treatment D
AUC(0-∞) (µg.h/mL)	33.5[3] (29.9-37.6) [51]	35.1[4] (32.0-38.6) [42]	ND[2]	ND[2]
AUC(0-t) (µg.h/mL)	31.9 (28.3-35.9) [55]	34.0 (31.0-37.2) [41]	ND[2]	ND[2]
AUC(0-τ) (µg.h/mL)	ND[2]	ND[2]	26.4 (24.3-28.7) [36]	24.0 (22.0-26.1) [37]
Cmax (µg/mL)	8.74 (8.03-9.51) [38]	7.67 (7.09-8.29) [35]	8.25 (7.57-8.99) [37]	6.69 (6.12-7.30) [38]
Cτ (µg/mL)	ND[2]	ND[2]	0.401 (0.359-0.447) [49]	0.442 (0.394-0.496) [52]
tmax (h)[1]	1.00 (0.48-2.50)	2.00 (0.73-5.00)	0.98 (0.50-3.00)	1.50 (0.73-5.00)

Source Data: Table 10.3 and Table 10.8
Treatment A: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered fasted.
Treatment B: Two FPV 700mg oral film-coated tablets administered fasted.
Treatment C: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered BID for 10 days; fasted PK.
Treatment D: Two FPV 700mg oral film-coated tablets administered BID for 10 days; fasted PK.
1. tmax was presented as median (range)
2. ND: not determined
3. N=71
4. N=72

Table 3 shows the plasma APV PK treatment comparisons.

Table 3: Plasma APV PK Treatment Comparisons in APV10024

Plasma APV PK Parameter	Ratio of Geometric Least Squares Means (90% CI)	
	Single Dose Part Treatment A/Treatment B	Repeat Dose Part Treatment C/Treatment D
AUC(0-∞)	0.951 (0.879, 1.03)	ND[1]
AUC(0-t)	0.933 (0.857, 1.02)	ND[1]
AUC(0-τ)	ND[1]	1.10 (1.03, 1.17)
Cmax	1.13 (1.06, 1.20)	1.23 (1.16, 1.31)
Cτ	ND[1]	0.905 (0.848, 0.966)
tmax[2]	-0.75 (-1.00, -0.60)	-0.49 (-0.64, -0.25)

Source Data: Table 10.5 and Table 10.10
Treatment A: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered fasted.
Treatment B: Two FPV 700mg oral film-coated tablets administered fasted.
Treatment C: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered BID for 10 days; fasted PK.
Treatment D: Two FPV 700mg oral film-coated tablets administered BID for 10 days; fasted PK.
1. ND: not determined
2. tmax: estimated median difference using Koch & Hauschke

The results from study **APV10024** were as follows (for details regarding the study design, please refer to the individual study report):

1) After single dose administration under fasted conditions, the suspension and film coated tablet showed similar $AUC_{0-\infty}$, however, the C_{max} from the suspension formulation was 13 % higher as compared to the tablet formulation.
2) After steady state dosing, both the formulation showed equivalent steady-state plasma APV $AUC_{0-\tau}$ and C_{τ}, however, suspension delivered a 23 % higher C_{max} compared to the tablet formulation.

A comparison of exposure parameters observed in the two biopharmaceutics studies (**APV10016** and **APV10024**) indicates that the exposure parameters (C_{max} and AUC) of the suspension and the tablet formulations observed in study **APV10024** were approximately double the exposures observed in study **APV10016**. The applicant indicates that demographics and assay cannot explain these differences. Based on the reviewer's assessment, the primary differences between the two studies is the sample size (n = 32 in APV10016 and N = 71 in APV10024) and *potential* inter-batch variability in the formulations used in the two studies. However, differences in sample size should primarily impact the confidence intervals and *potential* differences in batches are not expected to result in the magnitude of differences observed across the two studies. Therefore, the differences in exposure cannot be explained on the basis of the information currently available, however, since the studies were well controlled, the intra-study comparison of exposure parameters should still be valid.

The literature on the pharmacokinetics of amprenavir (after administration of fosamprenavir) was also reviewed in order to obtain information on systemic exposures of amprenavir (after administration of fosamprenavir) published by different research groups. The review article by Wire et. al. (Clinical Pharmacokinetics, 2006, 45 (2), 137-168) on the clinical pharmacokinetics and drug interactions of fosamprenavir suggested that the steady-state AUC_{0-12} (expected to be similar to $AUC_{0-\infty}$ of amprenavir after administration of a single 1400 mg dose of FPV) of amprenavir after administration of FPV 1400 mg BID to either healthy or HIV infected subjects ranged from 15.3-17.8 µg*hr/mL. The estimates (in the literature and currently approved label) of steady state AUC_{0-24} after administration of FPV 1400 mg BID were approximately 33 µg*hr/mL. Therefore, the published information suggests that the $AUC_{0-\infty}$ of amprenavir after administration of a single 1400 mg dose of FPV is expected to be ~16.5 µg*hr/mL, similar to the $AUC_{0-\infty}$ observed in APV10016.

Based on the results of study **APV10016** and **APV10024**, the applicant proposed the following labeling recommendation:

Adults should take the suspension without food to match exposure from clinical trials using tablets; pediatric patients should take the suspension with food.

The labeling recommendation for pediatric subjects (administration of suspension formulation with food) is included in order to improve adherence and tolerability. The

impact of food was taken into account (in terms of the doses administered/adjusted during the trial) in the two pivotal pediatric studies (**APV29005** and **APV20003**). Further, similar to the dosing recommendation of the tablets in adult patients (the tablets can be administered with or without food), the tablet formulation can be administered to the pediatric (adolescent) patients with or without food.

Objective # 2 (Pediatric Dosing)

To support dosing recommendations of un-boosted and low dose ritonavir-boosted FPV containing regimens in pediatric subjects 2-18 years of age, the applicant submitted 48-week safety, efficacy, and pharmacokinetic data from two ongoing, Phase II studies (**APV20003** and **APV29005**) that were pivotal for dose selection.

APV20003 was designed to evaluate the pharmacokinetics (PK), safety, and antiviral response of a once daily regimen of FPV/RTV in antiretroviral treatment (ART)-naïve and ART experienced subjects. The protocol was amended to allow protease inhibitor (PI)-experienced subjects to switch to a FPV/RTV BID regimen after data collected in PI-experienced adults (**APV30003**) showed (based on applicant's assessment) improved response from BID dosing.

Table 4 shows the major PK related conclusions from study APV20003.

Table 4: Major PK related conclusions from study APV20003

Age Range	Dosing Regimen (FPV/RTV)	PK Conclusion
2-5 years	30/6 mg/kg QD	30 % lower $AUC_{0-\tau}$, 34 % lower C_{max}, and 30 % lower C_τ as compared to values historically observed for adult subjects receiving FPV/RTV 1400/200 mg QD.
6-11 years	30/6 mg/kg QD	27 % lower $AUC_{0-\tau}$, 30 % lower C_{max}, and C_τ similar to values historically observed for adult subjects receiving FPV/RTV 1400/200 mg QD.
12-18 years	30/6 mg/kg QD or 1400/200 mg QD	Similar $AUC_{0-\tau}$ and C_{max}, and C_τ 20 % lower than values observed in adults receiving 1400/200 mg QD.

The subsequent study, **APV29005**, was designed to evaluate a twice-daily regimen of un-boosted FPV in PI-naïve subjects 2-5 years of age and twice-daily regimen of FPV/RTV in PI-naïve and PI-experienced subjects 2-18 years of age. Table 5 shows the major PK related conclusions from study APV29005.

Table 5: Major PK Related Conclusions from Study APV29005

Age Range	Dosing Regimen	PK Conclusion/Comment
2-5 years	FPV 40 mg/kg BID	37 % higher $AUC_{0-\tau}$, 29 % higher C_{max} and 96 % higher C_τ than historically observed in adults after administration of 1400 mg BID.
	FPV 30 mg/kg BID	11 % lower $AUC_{0-\tau}$, similar C_{max}, and 28 % higher C_τ than historically observed in adults after administration of 1400 mg BID.
	FPV/RTV BID	*No conclusion because PK data were available from only 2 of the 3 subjects enrolled in this cohort.*
6-11 years	FPV/RTV 15/3 mg/kg BID and 18/3 mg/kg BID	**15/3 mg/kg regimen:** 13 % lower $AUC_{0-\tau}$, 23 % lower C_{max} and similar C_τ compared to adults after administration of 700 mg/100 mg BID. **18/3 mg/kg regimen:** 26 % higher $AUC_{0-\tau}$ and similar C_{max} and C_τ for 18/3 mg/kg regimen as compared to the adult population after administration of 700 mg/100 mg BID.
12-18 years old	15/3 mg/kg BID and 700/100 mg BID	**15/3 mg/kg regimen:** 41 % lower $AUC_{0-\tau}$, 30 % lower C_{max} and 33 % lower C_τ compared to adults after administration of 700 mg/100 mg BID. **700/100 mg BID:** 20 % lower $AUC_{0-\tau}$, 23 % lower C_{max}, and 20 % lower C_τ than historically observed in adults after administration of 700 mg/100 mg BID.

In addition to studies **APV20003** and **APV29005**, the applicant is also conducting study **APV20002** to assess the FPV BID regimens (with or without low dose ritonavir) in subjects aged 4 weeks to < 2 years of age. [redacted] b(4)

Table 6 shows the doses **originally** proposed by the applicant based on the results of study **APV20003** and **APV29005**.

Table 6: Applicant's Proposed Doses in Pediatric Subjects (2-18 years)

Patient Population	Age	Lexiva Twice Daily	Lexiva/Ritonavir	
			Once Daily	Twice Daily
Therapy Naive	2-5 years	30 mg/kg	[redacted]	
	≥ 6 years	30 mg/kg#	[redacted]	18/3 mg/kg
PI Naïve	2-5 years	No dosing recommendation	[redacted]	
	≥ 6 years			18/3 mg/kg
PI Experienced	2-5 years	No dosing recommendation	No dosing recommendation	
	≥ 6 years			18/3 mg/kg

b(4)

*: Doses have not been evaluated in the clinical trial and are proposed based on modeling/simulation
#: Based on approved amprenavir pediatric dosage

The dose of un-boosted fosamprenavir in pediatric subjects ≥ 6 years of age (30 mg/kg BID) is based on the amprenavir exposures observed in studies PROB2004 and PROAB3004, the equivalency of amprenavir (in terms of molar equivalents) to fosamprenavir, and the relative bioavailability and food effect studies. These studies, previously submitted and reviewed, also supported the use of amprenavir in the treatment of HIV infected pediatric patients 4 years and above.

The doses identified with an asterisk (*) have **not** been evaluated in a clinical trial and are being proposed based on modeling/simulation. Although the systemic exposure (predicted based on modeling/simulation) in pediatric patients at the proposed doses is *expected* to be similar to the exposures observed in the adult population at the approved doses, **the safety profile of some of the proposed doses is currently unknown.** The Division of Antiviral Products (DAVP) requires safety data in pediatric patients at the proposed dose(s) or higher doses, therefore modeling/simulation information was not reviewed in detail. The doses for which the exposure and adequate safety data are available will be approved. Table 7 shows the final pediatric dosing information.

Table 7: Pediatric Dosing Information

Patient Population	Age	Lexiva Twice Daily (treatment naive)	Lexiva/Ritonavir (treatment naive or experienced)	
			Once Daily	Twice Daily
Therapy Naive	2-5 years	30 mg/kg	No dosing recommendation	No dosing recommendation
	≥ 6 years	30 mg/kg#	No dosing recommendation	18/3 mg/kg
PI Naïve	2-5 years	No dosing recommendation	No dosing recommendation	No dosing recommendation
	≥ 6 years		No dosing recommendation	18/3 mg/kg
PI Experienced	2-5 years	No dosing recommendation	No dosing recommendation	No dosing recommendation
	≥ 6 years			18/3 mg/kg

Objective # 3 (Dosing in Patients with Hepatic Impairment)

Table 8 shows the current labeling recommendations of amprenavir and fosamprenavir in subjects with different degrees of hepatic impairment.

Table 8: Current labeling recommendations of amprenavir and fosamprenavir in subjects with different degrees of hepatic impairment.

	Amprenavir		Fosamprenavir	
	Without Ritonavir	**With Ritonavir**	**Without Ritonavir**	**With Ritonavir**
Normal Hepatic Function	1200 mg BID	1200/200 mg QD or 600/100 mg BID	1400 mg BID	1400/200 mg QD or 700/100 mg BID
Mild Hepatic Impairment	450 mg BID	N/A	700 mg BID	N/A
Moderate Hepatic Impairment	450 mg BID	N/A	700 mg BID	N/A
Severe Hepatic Impairment	300 mg BID	N/A	N/A	N/A

Note: The shaded areas represent the dosing regimens for which the applicant is seeking approval either based on the results of study APV10017 (dosing recommendations of boosted fosamprenavir in subjects with mild and moderate hepatic impairment) or based on the results of study PROB1008 (dosing recommendation for un-boosted fosamprenavir in subjects with severe hepatic impairment).

Use of Boosted Fosamprenavir Regimens in Patients with Mild and Moderate Hepatic Impairment.

To support dosing recommendations of boosted FPV regimens in HIV infected subjects with mild, moderate, and severe hepatic impairment, the sponsor conducted study **APV10017**. This study was an open-label, parallel, 2-week, repeat-dose study. Table 9 shows the summary and statistical comparison of selected pharmacokinetic plasma APV pharmacokinetic parameters for **mild hepatic impairment** and normal hepatic function groups in APV10017.

Table 9: Summary and statistical comparison of selected pharmacokinetic plasma APV pharmacokinetic parameters for mild hepatic impairment and normal hepatic function groups in APV10017.

Plasma APV PK Parameter	Geometric Mean [95% CI] (CV b%)		GLS Mean Ratio [90% CI]
	Mild HI (Group A) N=10	Normal Hepatic Function (Group D) N=10	Mild HI vs Normal Hepatic Function
AUC(0-τ) (µg.h/mL)	46.6 [39.0, 55.5] (25)	38.1 [31.6, 46.0] (27)	1.22 [0.94, 1.59]
Cmax (µg/mL)	7.04 [5.72, 8.66] (30)	6.00 [4.97, 7.25] (27)	1.17 [0.90, 1.53]
Cτ (µg/mL)	2.38 [1.80, 3.15] (40)	2.62 [2.14, 3.21] (29)	0.91 [0.63, 1.32]
CL/F (mL/min)	215 [180, 256] (25)	262 [217, 316] (27)	0.82 [0.63, 1.07]
t1/2 (h)	7.69[1] [5.83, 10.7] (38)	6.44[1] [4.99, 8.32] (31)	1.23 [0.89, 1.69]

HI: Hepatic Impairment
Mild HI: Hepatic Fibrosis + Child Pugh Score of 5-6
Group A: FPV 700 mg BID + RTV 100 mg QD X 14 days
Group D: FPV 700 mg BID + RTV 100 mg BID X 14 days

Subjects with mild hepatic impairment receiving standard doses of FPV 700mg BID (administered as the FPV tablet) in combination with a reduced dosing frequency of RTV 100 mg QD had approximately 17-23 % higher plasma APV C_{max}, $AUC_{0-\tau}$, and $t_{1/2}$ values, 18 % lower CL/F, and similar C_τ values compared to subjects with normal hepatic function receiving FPV/RTV 700/100 mg BID. **Based on the results of the study, the applicant has proposed 700 mg BID + RTV 100 mg QD in treatment naïve or treatment experienced subjects with mild hepatic impairment. The proposed dose is acceptable.**

Table 10 shows the summary and statistical comparison of selected pharmacokinetic plasma APV pharmacokinetic parameters for **moderate hepatic impairment** and normal hepatic function groups in APV10017.

Table 10: Summary and statistical comparisons of selected plasma APV pharmacokinetic parameters for moderate hepatic impairment and normal hepatic function groups.

Plasma APV PK Parameter	Geometric Mean (95% CI) [CVb%] Moderate HI FPV BID/ RTV QD (Group B) N=10	Moderate HI FPV QD/ RTV QD (Group C) N=8	Normal Hepatic Function FPV BID/ RTV BID (Group D) N=10	GLS Mean Ratio (90% CI) Moderate HI vs Normal Hepatic Function Group B vs Group D	Group C vs Group D
Dose Normalized					
DN-AUC(0-τ) (µg.h/mL)	64.8 [46.5, 90.4] (49)	57.8 [42.1, 79.3] (39)	38.1 [31.6, 46.0] (27)	1.70 [1.31, 2.21]	1.51 [1.15, 2.00]
DN-Cmax (µg/mL)	10.2 [7.18, 14.5] (52)	6.68 [5.14, 8.70] (32)	6.00 [4.97, 7.25] (27)	1.70 [1.30, 2.22]	1.11 [0.84, 1.48]
DN-Cτ (µg/mL)	2.63 [1.73, 3.99] (64)	0.93 [0.53, 1.62] (75)	2.62 [2.14, 3.21] (29)	1.00 [0.69, 1.45]	0.35 [0.24, 0.53]
Observed					
AUC(0-τ) (µg.h/mL)	27.8 [19.9, 38.7] (49)	57.8 [42.1, 79.3] (39)	38.1 [31.6, 46.0] (27)	0.73 [0.56, 0.95]	1.51 [1.15, 2.00]
Cavg (µg/mL)	2.32 [1.66, 3.23] (49)	2.41 [1.75, 3.30] (39)	3.18 [2.64, 3.83] (27)	0.73 [0.56, 0.95]	0.76 [0.57, 1.00]
Cmax (µg/mL)	4.38 [3.08, 6.22] (52)	6.68 [5.14, 8.70] (32)	6.00 [4.97, 7.25] (27)	0.73 [0.56, 0.95]	1.11 [0.84, 1.48]
Cτ (µg/mL)	1.13 [0.74, 1.71] (64)	0.93 [0.53, 1.62] (75)	2.62 [2.14, 3.21] (29)	0.43 [0.30, 0.62]	0.35 [0.24, 0.53]
CL/F (mL/min)	154 [111, 215] (49)	173 [126, 238] (39)	262 [217, 316] (27)	0.59 [0.45, 0.76]	0.66 [0.50, 0.87]
t1/2 (h)	6.78[1] [4.60, 10.0] (49)	7.96 [5.93, 10.7] (36)	6.44[1] [4.99, 8.32] (31)	1.05 [0.76, 1.45]	1.23 [0.90, 1.70]

HI: Hepatic Impairment
Moderate HI: Hepatic Fibrosis +Child Pugh Score of 7-9
Group B: FPV 300 mg BID + RTV 100 mg QD X 14 days
Group C: FPV 700 mg QD + RTV 100 mg QD X 14 days
Group D: FPV 700 mg BID + RTV 100 mg BID X 14 days

The similarity in CL/F and dose normalized C_{avg} between the two groups suggests that the PK is expected to be similar for both dosing regimens. **Therefore, FPV 450 mg BID + RTV 100 mg QD is predicted to deliver average $AUC_{0-\tau}$ (41.7 µg*hr/mL) similar to subjects with normal hepatic function receiving the standard FPV/RTV 700 mg/100 mg BID regimen. The predicted steady state total (bound + unbound) C_τ levels (~1.7 µg/mL) after administration of 450 mg BID + RTV 100 mg QD are expected to be lower than the total (bound + unbound) C_τ levels (2.62 µg/mL) after administration of 700 mg BID + 100 mg BID, however, the *unbound* plasma APV C_τ after administration of 450 mg BID + 100 mg QD is expected to be ~70 % higher (due to higher unbound fraction in subjects with hepatic impairment). Therefore, the antiviral efficacy (which is primarily governed by the unbound levels of the drug) is**

not expected to be lower in subjects with moderate hepatic impairment after administration of FPV 450 mg BID + 100 mg RTV QD as compared to subjects with normal hepatic function after administration of 700 mg BID + RTV 100 mg BID. The applicant proposed a dose of 450 mg BID + RTV 100 mg QD in treatment naïve or treatment experienced subjects with moderate hepatic impairment. The proposed dose is acceptable.

Use of Unboosted Fosamprenavir Regimen in Patients with Severe Hepatic Impairment

Severe Hepatic Impairment

PROB 1008 (open label, parallel, single dose study of APV 600 mg (equivalent to FPV 700 mg) was conducted in HIV seronegative subjects (n = 30) with mild, moderate, and severe hepatic impairment to matched control subjects with normal hepatic function. Based on the review (previously conducted) of the study, 300 mg BID dose of amprenavir (75 % lower than the approved 1200 mg BID un-boosted regimen for subjects with normal hepatic function) was found to be acceptable for subjects with severe hepatic impairment.

A FPV 700 mg BID dosage regimen for administration to patients with mild and moderate hepatic impairment was previously approved. Although a FPV 350 mg BID regimen (75 % lower than the approved 1400 mg BID unboosted regimen for subjects with normal hepatic function) could have been approved for subjects with severe hepatic impairment, this dose could not be achieved with the available 700 mg tablet formulation. Therefore, on the basis of the approved, un-boosted, amprenavir dose in subjects with severe hepatic impairment and the equivalency of 600 mg amprenavir (in terms of molar equivalents) to 700 mg fosamprenavir, **the applicant has proposed an un-boosted fosamprenavir dose of 350 mg BID in therapy naïve patients with severe hepatic impairment. The proposed dose is acceptable. There are no data on the use of LEXIVA in combination with ritonavir in patients (therapy naïve or experienced) with severe hepatic impairment.**

Vikram Arya, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 4

Concurrence:

Kellie S. Reynolds, Pharm. D
Team Leader
Division of Clinical Pharmacology 4

2 Question based review (QBR)

2.1 General Attributes of The drug

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 as they relate to the clinical pharmacology and biopharmaceutics review?

Fosamprenavir (Lexiva, fosamprenavir calcium, FPV), is the phosphate ester pro-drug of the HIV protease inhibitor, amprenavir (Agenerase, APV). The molecular formula of fosamprenavir calcium is $C_{25}H_{34}CaN_3O_9PS$ and the molecular weight is 623.7. FPV is rapidly and extensively converted to amprenavir ($C_{25}H_{35}N_3O_6S$; 505.64) by the alkaline phosphatase at the apical endothelium of the intestinal membrane.

Lexiva oral suspension is a white to off–white suspension which has a characteristic bubblegum odor. The product contains 50 mg/mL of fosamprenavir as the calcium salt, equivalent to approximately 43 mg of amprenavir, and is packaged into 8 oz. white, round [redacted] bottles with [redacted] child-resistant closures at a fill volume of 225 mL. Table 1 shows the composition of the Lexiva oral suspension. b(4)

Table 1: Composition of Lexiva Oral Suspension

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

Note:
1. Equivalent to 50 mg of fosamprenavir. The stated quantity of fosamprenavir calcium assumes a nominal water content of five moles and may be adjusted based on purity.

b(4)

As compared to the approved amprenavir solution (15 mg/mL), FPV oral suspension contains lower concentrations of propylene glycol ([redacted] in fosamprenavir suspension compared to 550 mg/mL in amprenavir solution). In addition, the FPV oral suspension contains no Vitamin E (compared to 46 IU/mL for amprenavir solution) and is more concentrated (50 mg/mL compared with 15 mg/mL), thereby reducing the dosing volumes. b(4)

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.

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

Dosing in Subjects with Hepatic Impairment

The proposed oral doses in subjects with hepatic impairment are as follows:

Mild Hepatic Impairment (Child-Pugh Score 5-6): FPV 700 mg BID + RTV 100 mg QD

Moderate Hepatic Impairment (Child-Pugh Score 7-9): FPV 450 mg BID + RTV 100 mg QD

Severe hepatic impairment (Child Pugh Score 10-12): FPV 350 mg BID.

The proposed dose of un-boosted fosamprenavir in subjects with severe hepatic impairment is based on the previously conducted PK study with amprenavir **(PROB1008)** in subjects with mild, moderate, and severe hepatic impairment.

Dosing in Pediatric Subjects

Table 2 shows the pediatric dosing information originally proposed by the applicant.

Table 2: Applicant's Originally Proposed Doses in Pediatric Subjects (2-18 years)

Patient Population	Age	Lexiva Twice Daily	Lexiva/Ritonavir	
			Once Daily	Twice Daily
Therapy Naive	2-5 years	30 mg/kg	[redacted]	
	≥ 6 years	30 mg/kg#	[redacted]	18/3 mg/kg
PI Naïve	2-5 years	No dosing recommendation	[redacted]	
	≥ 6 years		[redacted]	18/3 mg/kg
PI Experienced	2-5 years	No dosing recommendation	No dosing recommendation	[redacted]
	≥ 6 years			18/3 mg/kg

b(4)

*: Doses have not been evaluated in the clinical trial and are proposed based on modeling/simulation
#: Based on approved amprenavir pediatric dosage

As some of the doses evaluated in the clinical trials provided lower systemic exposures than the target adult exposures (at the approved doses), higher doses (as proposed by the applicant in table 2 and identified by asterisk) will be required to match the adult exposures. However, the safety profile at these higher doses is unknown. Therefore, only those doses which provided systemic exposure similar to adult exposure and for

which adequate safety data is available, will be approved. Table 3 shows the final pediatric dosing information.

Table 3: Final Pediatric Dosing Information

Patient Population	Age	Lexiva Twice Daily	Lexiva/Ritonavir	
			Once Daily	Twice Daily
Therapy Naive	2-5 years	30 mg/kg	No dosing recommendation	No dosing recommendation
	≥ 6 years	30 mg/kg[#]	No dosing recommendation	18/3 mg/kg
PI Naïve	2-5 years	No dosing recommendation	No dosing recommendation	No dosing recommendation
	≥ 6 years		No dosing recommendation	18/3 mg/kg
PI Experienced	2-5 years	No dosing recommendation	No dosing recommendation	No dosing recommendation
	≥ 6 years			18/3 mg/kg

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 studies were designed by the applicant to meet three specific regulatory objectives:

- Demonstrate the similarity in exposures between the Lexiva suspension and tablet formulations.
- Determine the dosing recommendations of boosted fosamprenavir in subjects with mild and moderate hepatic impairment.
- Determine the pharmacokinetics of un-boosted and ritonavir-boosted fosamprenavir in pediatric subjects.

To meet objective # 1, the applicant conducted the following two studies:

APV10016

A Pivotal, Phase I, Single Dose, Open-Label, Randomized, Four Period, Balanced Crossover Study to Assess the Relative Bioavailability of the GW433908 (Fosamprenavir; FPV) Oral Suspension and Oral Film-Coated 700 mg Tablet Formulations and the Effect of Food on the Bioavailability of these Formulations in Healthy Adult Subjects.

APV10024

A Pivotal, Phase I, Open-Label, Randomized, Four Period, Two-Part, Crossover Study to Assess the Relative Bioavailability of the Fosamprenavir 50 mg/mL Oral Suspension and 700 mg Oral Film-Coated Tablet Formulations Following Administration of Single 1400 mg Doses and Following Administration of 1400 mg BID for 10 days in Healthy Adult Subjects.

The primary objectives of both the studies were to determine the single dose pharmacokinetics of fosamprenavir after administration of the suspension and tablet formulation. In addition to the aforementioned objectives, study APV10016 assessed the effect of food on the pharmacokinetics of fosamprenavir after administration of the suspension and tablet formulation and study APV10024 assessed the steady-state pharmacokinetics of fosamprenavir after administration of the suspension and tablet formulation.

To meet objective # 2, the applicant conducted the following study:

APV10017

A Phase I, Parallel, Open-Label, Multicenter, Two-Week, Repeat-Dose Study Evaluating Plasma Amprenavir Pharmacokinetics in HIV-1 Infected Adult Subjects with Mild, Moderate, or Severe Hepatic Impairment Receiving Fosamprenavir +Ritonavir Compared to Matched Control Subjects with Normal Hepatic Function: Analyses of Mild and Moderate Hepatic Impairment.

The primary goal of the study was to determine the pharmacokinetics of ritonavir-boosted fosamprenavir in subjects with mild and moderate hepatic impairment.

To meet objective # 3, the applicant conducted the following two studies:

APV20003

A 48 Week, Phase II, Open-Label, Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Fosamprenavir/Ritonavir QD and Fosamprenavir/Ritonvir BID when Administered to HIV-1 Infected, Antiretroviral Naïve and Experienced, Pediatric Subjects 2 to 18 Years Old.

APV29005

A 48 Week, Phase II, Non-Comparative, Open-Label, Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of GW433908 (Fosamprenavir)/Ritonavir BID when Administered to HIV-1 Infected, PI-naïve and Experienced, Pediatric Subjects, 2 to 18 Years Old and of FPV BID Administered to PI-naïve, Pediatric Subjects 2 to < 6 Years Old.

The objective of both the studies was to assess the pharmacokinetics of fosamprenavir in pediatric subjects 2-18 years old.

For details regarding the study design, please refer to the individual study reports.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Viral load and CD4+ cell count are accepted as surrogate markers for efficacy in trials with ARV agents. However, the primary goal of studies in pediatric subjects and subjects with hepatic impairment were to match the systemic exposures observed in the adult population at the approved doses and to assess the safety of the various un-boosted and ritonavir boosted fosamprenavir dosing regimens. Although the antiviral efficacy of the various FPV dosing regimens was assessed in the pediatric studies, no efficacy related conclusions can be drawn due to the low sample size, within study switch of regimens (from QD to BID), and the adverse events related discontinuations (Please refer to Medical Officer's Review for further details).

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

Yes, the sponsor quantified the appropriate moieties in all the clinical pharmacology studies.

2.2.4. Exposure-Response

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

A number of previously conducted, well controlled studies have established dose/concentration *vs* response relationships between the fosamprenavir (or amprenavir) dose/concentration with the desired clinical response (sustained virologic suppression). Therefore, the primary goal of the studies was to determine dose(s) and regimens that will result in exposures similar to the exposures previously observed in adult studies at the approved doses (shown in table 4 in the response to question 2.2.5). As the progression of HIV infection is similar between adult and pediatric population, a similarity in plasma exposures would indicate similar virologic response.

2.2.4.2. What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The amount of data available is not adequate to derive dose-response or concentration-response relationships for safety. However, GI related adverse events such as vomiting and diarrhea occurred more frequently in pediatric patients receiving FPV, with or without ritonavir, as compared to adult subjects.

2.2.4.3. Does fosamprenavir prolong QT or QTc interval?

Not applicable to this NDA.

2.2.4.4. Is 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?

The sponsor selected doses for the hepatic impairment studies and the pediatric studies on the basis of amprenavir pharmacokinetic data from previous studies, with the goal of matching the systemic exposures to the systemic exposures observed in adults at the approved dose.

A number of doses proposed by the applicant in the pediatric subjects are higher than the doses evaluated the pivotal pediatric trials (APV20003 and APV29005). As some of the doses evaluated in the clinical trials provided lower systemic exposures than the target adult exposures (at the approved adult doses), higher doses (than the doses evaluated in the pivotal pediatric studies) will be required to match the adult exposures. However, the safety profile at these higher doses is unknown. Therefore, only those doses which provided systemic exposure similar to adult exposure and for which adequate safety data is available, will be approved.

2.2.5. What are the PK characteristics of fosamprenavir?

Table 4 (extracted from the fosamprenavir package insert) shows the PK parameters of amprenavir after administration of various fosamprenavir regimens to HIV infected adults. These parameters serve as the references for the proposed regimens in pediatric patients and patients with hepatic impairment.

Table 4: Geometric Mean (95 % CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters.

Regimen	C_{max} (mcg/mL)	T_{max} (hours)*	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 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)

*Data shown are median (range).

Note: All the regimens shown in table 4 are approved for therapy naïve subjects, however, The LEXIVA 700 mg b.i.d. + ritonavir 100 mg b.i.d. regimen is approved only for HIV infected therapy experienced subjects.

2.3 Intrinsic Factors

2.3.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2. Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1. Pediatric Patients

Based on the higher rate of clearance in pediatric subjects, the pediatric subjects will need higher doses (when normalized to mg/kg) in order to match the systemic exposures in adults at the approved doses. Therefore, the goal of the pediatric studies was to evaluate the doses/dosing regimens that would provide systemic exposures similar to the adult systemic exposures at the approved adult doses. Please refer to the table of PK conclusions (table 4 and table 5 in the executive summary section) for further information.

2.3.2.2. Hepatic Impairment

The following dosing regimens are recommended for subjects with hepatic impairment. Please refer to tables 8, 9, and 10 in the executive summary for further information.

Mild Hepatic Impairment (Child-Pugh Score 5-6): FPV 700 mg BID + RTV 100 mg QD.

Moderate Hepatic Impairment (Child-Pugh Score 7-9): FPV 450 mg BID + RTV 100 mg QD.

Severe hepatic impairment (Child Pugh Score 10-12): FPV 350 mg BID.

The proposed dose of un-boosted fosamprenavir in subjects with severe hepatic impairment is based on the systemic exposures observed after oral administration of amprenavir to subjects with mild, moderate, and severe hepatic impairment.

2.4 Extrinsic Factors:

2.4.1. What extrinsic factors influence dose-exposure and/or –response, and what is the impact of any differences in exposure on response?

The extrinsic factors that were considered for their potential effect on the pharmacokinetics of fosamprenavir were the impact of concomitant food intake (described in section 2.5.3.).

The drug-drug interactions of FPV are mediated by CYP3A, hence, the drug-drug interaction profile should be similar in adult and pediatric subjects.

2.5 General Biopharmaceutics

2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The pH solubility profile of fosamprenavir calcium is that of an ampholyte (weak acid/weak base) below pH 3.3. The solubility decreases from 10 mg/mL at pH 3.3 to 3 mg/mL at pH 1.7. The solubility above pH 3.3 decreases to 0.3 mg/mL at pH 7.5.

For dissolution related information, please refer to the Chemistry review.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

Not Applicable to this NDA

2.5.2.1. What data support or do not support a waiver of *in vivo* BE data?

Not applicable to this NDA

2.5.2.2. What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90 % CI using equivalence limits of 80-125 %?

The applicant conducted two studies (**APV10016** and **APV10024**) in healthy adults to demonstrate the similarity in systemic exposures (C_{max} and AUC) after administration of the suspension formulation and tablet.

The results of study APV10016 showed that APV C_{max} after administration of suspension formulation was 14.5 % higher as compared to tablets. This increase in C_{max} is not expected to be clinically relevant.

The results of study APV10024 showed higher mean C_{max} (13 % after single dose and 23 % after multiple dose) after administration of the suspension formulation as compared to the tablet formulation. This increase in C_{max} is not expected to be clinically relevant.

2.5.3 What is the effect of food on the bioavailability (BA) of amprenavir from the dosage form? What dosing recommendation should be made, if any, regarding

administration of the product in relation to meals or meal types?

The effect of food on the pharmacokinetics of the amprenavir (after administration of a single 1400 mg dose of fosamprenavir as suspension and tablet) was assessed in study APV10016. Table 5 and 6 show the impact of food on the pharmacokinetics of amprenavir after administration of the tablet formulation and suspension formulation respectively.

Table 5: Statistical analysis of the pharmacokinetic parameters of APV observed after treatment A (tablet administered under fasting conditions) and treatment B (tablet administered under fed conditions)

Plasma APV PK Parameter	Geometric LS Mean		Ratio (90% CI) B/A
	Tablet Fasted (Treatment A)	Tablet Fed (Treatment B)	
AUC_{∞} (µg.h/mL)	16.52	15.93	0.964 (0.846-1.098)
AUC_{last} (µg.h/mL)	16.14	15.38	0.953 (0.837-1.086)
C_{max} (µg/mL)	4.03	4.44	1.102 (0.973-1.247)
$t_{½}$ (h)	4.02	5.21	1.296 (1.116-1.505)
t_{max} (h)	1.83	2.42	1.326 (1.113-1.539)
Treatment A: Two GW433908 oral film-coated 700mg tablets administered fasted. Treatment B: Two GW433908 oral film-coated 700mg tablets administered with food.			

a. t_{max} is presented as Geometric LS mean and ratio of the Geometric LS means.

Table 6: Statistical analysis of the pharmacokinetic parameters of APV observed after treatment C (suspension administered under fasting conditions) and treatment D (suspension administered under fed conditions)

Plasma APV PK Parameter	Geometric LS Mean		Ratio (90% CI) D/C
	Suspension Fasted (Treatment C)	Suspension Fed (Treatment D)	
AUC_{∞}(µg.h/mL)	15.86	11.40	0.719 (0.631-0.819)
AUC_{last}(µg.h/mL)	15.48	11.03	0.713 (0.626-0.812)
C_{max} (µg/mL)	4.62	2.50	0.542 (0.479-0.614)
$t_{½}$ (h)	4.25	4.70	1.107 (0.954-1.286)
t_{max} (h)	1.16	1.99	1.720 (1.383-2.056)
Treatment C: 28mL of 50mg/mL GW433908 oral suspension administered fasted. Treatment D: 28mL of 50mg/mL GW433908 oral suspension administered with food.			

a. t_{max} is presented as Geometric LS mean and ratio of the Geometric LS means.

The results showed that administration of the tablet with high-fat breakfast resulted in equivalent plasma AUC and C_{max} as compared to exposures under fasted conditions. The results in this study with the tablet formulation were similar (in terms of absence of food effect after administration of the tablet formulation) to previous studies designed to assess the effect of food on the tablet formulation.

The administration of the suspension formulation with high-fat breakfast decreased APV AUC and C_{max} values by 28 % and 46 % as compared to exposures under fasted conditions. This decrease in systemic exposures can have an impact on the efficacy of

amprenavir, therefore, the label will recommend administration of the suspension formulation to adult subjects under fasted conditions. The tablet formulation can be taken with or without food (consistent with the current labeling recommendation).

The pediatric subjects will be recommended to take the suspension formulation under fed state. The labeling recommendation for pediatric subjects (administration of suspension formulation with food) is included in order to improve adherence and tolerability. The impact of food was taken into account (in terms of the doses administered/adjusted during the trial) in the two pivotal pediatric studies (**APV29005** and **APV20003**). Further, similar to the dosing recommendation of the tablets in adult patients (the tablets can be administered with or without food), the tablet formulation can be administered to the pediatric (adolescent) patients with or without food.

2.6 Analytical Section

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

The active moities were identified and measured in the plasma by using validated LC/MS/MS methods.

2.6.2. Which metabolites have been selected for analysis and why?

No metabolites were selected for analysis

2.6.3. 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 and ritonavir. Although measurement of free concentrations of both moieties may be more clinically relevant, it is standard to measure total concentrations of protease inhibitors.

In the hepatic impairment study (**APV10017**), the protein binding was determined to assess the free concentrations in subjects with normal hepatic function and subjects with different degree of hepatic impairment.

2.6.4 What bioanalytical methods are used to assess concentrations?

Plasma samples were analyzed for APV by Worldwide Bioanalysis-Research Triangle Park (RTP), NC using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography with [redacted] (HPLC/MS/MS) analysis. The lower limit of quantification was 10 ng/mL using a 100 µL aliquot of human plasma. The higher limit of quantification (HLQ) was 10,000 ng/mL. b(4)

These analytical methods are acceptable.

3. Labeling Recommendations

(The following sections of the final label reflect edits suggested by the Clinical Pharmacology Review Team).

DOSAGE AND ADMINISTRATION

Pediatric Patients (>2 to 18 years of age)

The recommended dosage of LEXIVA in patients ≥2 years of age should be calculated based on body weight (kg) and should not exceed the recommended adult dose. The data are insufficient to recommend: (1) once-daily dosing of LEXIVA alone or in combination with ritonavir, and (2) any dosing of LEXIVA in therapy-experienced patients 2 to 5 years of age.

Therapy-naive 2 to 5 years of age: LEXIVA Oral Suspension 30 mg/kg twice daily, not to exceed the adult dose of LEXIVA 1,400 mg twice daily.

Therapy-naive ≥ 6 years of age: either LEXIVA Oral Suspension 30 mg/kg twice daily not to exceed the adult dose of LEXIVA 1,400 mg twice daily or LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg twice daily not to exceed the adult dose of LEXIVA 700 mg plus ritonavir 100 mg twice daily.

Therapy-experienced ≥ 6 years of age: LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg administered twice daily not to exceed the adult dose of LEXIVA 700 mg plus ritonavir 100 mg twice daily.

When administered without ritonavir, the adult regimen of LEXIVA Tablets 1,400 mg twice daily may be used for pediatric patients weighing at least 47 kg. When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg.

Patients with Hepatic Impairment

Mild Hepatic Impairment (Child-Pugh score ranging from 5 to 6): LEXIVA should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naive) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced).

Moderate Hepatic Impairment (Child-Pugh score ranging from 7 to 9): LEXIVA should be used with caution at a reduced dosage of 700 mg twice daily (therapy-naive) without ritonavir, or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced).

Severe Hepatic Impairment (Child-Pugh score ranging from 10 to 12): LEXIVA should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir (therapy-naive). There are no data on the use of LEXIVA in combination with ritonavir in patients with severe hepatic impairment.

CLINICAL PHARMACOLOGY

Absorption and Bioavailability

After administration of a single 1400 mg dose in the fasted state, LEXIVA Oral Suspension (50 mg/mL) and LEXIVA Tablets (700 mg) provided similar amprenavir exposures (AUC), however, the C_{max} of amprenavir after administration of the suspension formulation was 14.5 % higher compared to the tablet.

Special Populations

Hepatic Impairment: The pharmacokinetics of amprenavir have been studied after the administration of LEXIVA in combination with ritonavir to adult HIV-1-infected patients with mild and moderate hepatic impairment. Following 2 weeks of dosing with LEXIVA plus ritonavir, the AUC of amprenavir was increased by approximately 22 % in patients with mild hepatic impairment and by approximately 70 % in patients with moderate hepatic impairment compared with HIV-1-infected patients with normal hepatic function. Protein binding of amprenavir was decreased in both mild and moderate hepatic impairment, with the unbound fraction at 2 hours (approximate C_{max}) increasing by 18 % to 57 % and the unbound fraction at the end of the dosing interval (C_{min}) increasing 50 % to 102 %.

Pediatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA Oral Suspension and LEXIVA Tablets, with or without ritonavir, have been evaluated in 124 patients 2 to 18 years of age. Pharmacokinetic parameters for LEXIVA administered with food and with or without ritonavir in this patient population are provided in Tables 9 and 10 below.

Table 9. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters in Pediatric Patients Receiving LEXIVA 30 mg/kg Twice Daily

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 10. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters in Pediatric and Adolescent Patients Receiving LEXIVA Plus Ritonavir Twice Daily

	6 to 11 Years		12 to 18 Years	
Parameter	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)

Drug Interactions

In table 7.3 (Established and Other Potentially Significant Drug Interactions), under HMG-CoA reductase inhibitor, rosuvastatin was added to reflect the potential increase in rosuvastatin exposure when co-administered with Lexiva/ritonavir.

In addition to the changes indicated above, the applicant included the information related to drug-drug interaction pertaining to Kaletra, Tenofovir, Abacavir, and Methadone in the drug-drug interaction tables. In the previously approved package insert, the information related to these drug-drug interaction studies was included in the text format.

4. Appendices

4.1 Individual Study Review

APV10016

1. Title

A Pivotal, Phase I, Single Dose, Open-Label, Randomized, Four Period, Balanced Crossover Study to Assess the Relative Bioavailability of the GW433908 (Fosamprenavir; FPV) Oral Suspension and Oral Film-Coated 700 mg Tablet Formulations and the Effect of Food on the Bioavailability of these Formulations in Healthy Adult Subjects.

2. Objectives

The objectives of this trial were:

- To assess the relative bioavailability of fosamprenavir oral suspension and oral film-coated 700mg tablet formulation.
- To assess the effect of food on the bioavailability of fosamprenavir oral suspension formulation.
- To assess the effect of food on the bioavailability of the GW433908 oral 700mg tablet formulation.

3. Study Design

APV10016 was a pivotal, Phase I, single-dose, open-label, randomized, four period, balanced crossover study conducted at a single study center in the US. Thirty-six healthy adult subjects were planned to be enrolled to obtain a minimum of 30 evaluable subjects. If more than 6 subjects withdrew from the study before completing all 4 periods, additional subjects were to be enrolled as replacement subjects to attain at least 30 evaluable subjects. Table 1 shows the randomization scheme:

Table 1: Randomization Scheme Used in Study APV10016

Treatment Sequence	Sample Size	Period 1	Period 2	Period 3	Period 4
1	9	Treatment A	Treatment D	Treatment B	Treatment C
2	9	Treatment B	Treatment A	Treatment C	Treatment D
3	9	Treatment C	Treatment B	Treatment D	Treatment A
4	9	Treatment D	Treatment C	Treatment A	Treatment B
Treatment A = Two GW433908 oral film-coated 700mg tablets[a] administered fasted. Treatment B = Two GW433908 oral film-coated 700mg tablets[a] administered with food. Treatment C = 28mL of the 50mg/mL GW433908 oral suspension[b] administered fasted Treatment D = 28mL of the 50mg/mL GW433908 oral suspension[b] administered with food.					

a Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.
b The 50mg/mL GW433908 oral suspension is the molar equivalent of 43.2mg/mL APV.

For each of the four treatment periods, subjects checked into the study center on the day prior to the dosing and completed the check-in assessments. The investigator or designee administered each dose of investigational product with 240mL (8oz) of water to each subject at each of the four treatment periods (separated by a 4-7 days washout period). The bottle containing the suspension formulation was shaken well for at least 20 seconds immediately prior to measuring each dose of the oral suspension and twenty-eight milliliters of the oral suspension (50 mg/mL) was measured using three 10mL syringes.

For the fasted treatments, (treatments A and C), subjects were required to fast 10 hours before administration of study drug. Water was permitted during the fast, except for 1 hour prior to dosing. Each subject took 240mL (8 oz) of water with the study drug and fasted for an additional 4 hours after dosing.

For the fed treatments, (treatments B and D), subjects were required to fast 10h before administration of a standard meal (to be ingested within 30 minutes). Water was permitted during the fast, except for 1h prior to dosing. The study drug was administered with 240 mL of water within 5 minutes after completion of meal. The standard meal comprised of the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk.

Reviewer's Note Regarding Meal

The meal consumed by the study participants is representative of the standard meal (in terms of calorific content and fat content) used for food effect studies.

4. Rationale for Doses Used in the Trial

1400 mg is the highest approved (unit) dose of fosamprenavir.

5. Drugs Used in the Trial

Tablet

Each 700mg tablet contained 600mg APV molar equivalents. The tablets used in the study are the approved fosamprenavir 700 mg tablets.

Suspension

The GW433908 50mg/mL suspension was a white to off-white suspension for oral administration. **Each mL of suspension contained 50mg of the APV pro-drug GW433908, equivalent to 43.2mg/mL of APV.** The suspension contained the following inactive ingredients: hydroxypropylmethyl cellulose, polysorbate 80, methylparaben, propylparaben, propylene glycol, sucralose, calcium chloride, flavors and purified water. The GW433908 oral suspension was manufactured by GlaxoSmithKline in Mississauga, Ontario, Canada. The batch number of the formulation was 2A703. The formulation used in this trial was identical to the to-be-marketed formulation.

6. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Seventeen (17) serial whole blood samples for bio-analysis of plasma APV and GW433908 concentrations were collected (a total of 68 samples per subject; each sample was 2.7 mL) over 24 hrs in each of the four periods at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours.

Bioanalysis

Plasma PK samples were analyzed for APV by [redacted] The samples were quantified by LC/MS/MS assay. The lower limit of quantification for APV was 10 ng/mL. The validated range for the calibration curve for amprenavir was [redacted] The quality control samples were prepared for amprenavir at 10, 35, 1000, 8500, and 10, 000 ng/mL and were considered acceptable if they deviated by no more than [redacted] from the original concentration. The average accuracy (bias) values calculated from QC samples from four validation runs ranged from [redacted] The average within run precision (CV) and between-run precision results calculated from the QC samples from the four validation runs were [redacted]

b(4)

Reviewer's Note

The assay methodology is acceptable.

Pharmacokinetic Assessments

PK analysis of plasma APV concentration-time data was conducted using the non-compartmental Model 200 (for extravascular administration) of WinNonlin, Version 3.1, computer software (Pharsight Corporation, Mountain View, CA). Actual sample collection times were used in the APV PK analysis. Plasma APV concentrations below the limit of quantification prior to the first measurable concentration were considered to be equal to zero when conducting the PK analysis. Other APV BLQ values were excluded from pharmacokinetic analysis if the associated sampling time followed the time of the last measurable concentration during the sample collection period or if the value was embedded between two adjacent quantifiable values. When two or more consecutive BLQ values followed a measurable concentration, these values and any subsequent quantifiable values were excluded from the pharmacokinetic analysis.

Statistical Analysis

The PK dataset for the statistical analysis of the amprenavir pharmacokinetic parameters was based on the PK summary population (PK summary population included subjects

who had plasma APV PK parameter estimates for all 4 periods). Plasma APV AUC_{∞}, AUC_{last}, and C_{max} were log-transformed prior to the primary analyses and treatment comparisons were expressed as ratios on the original scale. Table 2 shows the primary treatment comparisons:

Table 2: Primary Treatment Comparisons for Amprenavir Pharmacokinetic Parameters

Treatment	Reference
Treatment C	Treatment A
Treatment B	Treatment A
Treatment D	Treatment C

Treatment A = Two GW433908 oral film-coated 700mg tablets[a] administered fasted.
Treatment B = Two GW433908 oral film-coated 700mg tablets[a] administered with food.
Treatment C = 28mL of the 50mg/mL GW433908 oral suspension[b] administered fasted
Treatment D = 28mL of the 50mg/mL GW433908 oral suspension[b] administered with food.

a Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.
b The 50mg/mL GW433908 oral suspension is the molar equivalent of 43.2mg/mL APV.

Bioequivalence was concluded if the 90 % CI ratio for the geometric least square (GLS) means fell within the 80-125 % range for C_{max}, AUC_{last}, and AUC_{∞}.

Analysis of variance (ANOVA), considering treatment sequence, period, and treatment as fixed effects and subject within sequence as a random effect, was performed using SAS (Version 6.12) Mixed Linear Models procedure to assess the relative bioavailability of APV from GW433908 oral film-coated tablet and oral suspension formulations and to assess the effect of food on these formulations. Carryover effect was assessed by examination of the pre-dose plasma APV concentrations of Periods 2, 3, and 4.

7. Results

7.1 Subject Disposition

40 subjects were enrolled and received at least one dose of the study drug. 32 subjects completed the study. Eight subjects prematurely withdrew from the study; two subjects during Treatment A (one subject withdrew consent and one subject withdrew from the study due to adverse events not related to the study drug), one subject during Treatment B (withdrew from the study due to adverse events not related to the study drug), two subjects from Treatment C (one subject withdrew consent and one subject withdrew from the study due to positive urine drug screen) and three subjects from Treatment D (one subject withdrew consent and two subjects withdrew from the study due to positive drug screen).

Table 3 shows the demographics of the study.

Table 3: Demographics of Study APV 10016

Characteristic	Sequence				Total
	1 (n = 8)	2 (n = 8)	3 (n = 8)	4 (n = 8)	32
Gender (Male/Female)	6/2	7/1	7/1	5/3	25/7
Age (yrs) (mean ± sd)	34.3 ± 7.1	26.4 ± 5.3	30.6 ± 7.8	35.4 ± 9.0	31.7 ± 7.9
Height (cm) (mean ± sd)	174.9 ±16.0	177.9 ± 5.6	174.4 ± 9.4	170 ± 9.5	174.3 ± 10.6
Weight (kg) (mean ± sd)	76.8 ±18.6	74.4 ±12.5	77.7 ±11.4	74.2 ±12.8	75.79 ±13.5

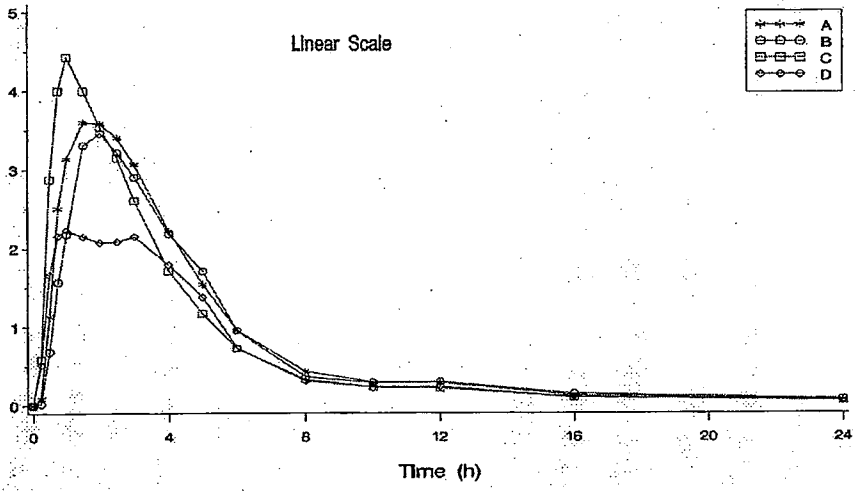
Reviewer's Note Regarding Demographics

The sponsor indicated that the PK population included all subjects who underwent plasma PK sampling during the study (37 subjects in treatment A, 35 subjects in treatment B, 35 subjects in treatment C and 36 subjects in treatment D). However, the PK summary population included only subjects (N = 32) who had plasma APV PK parameter estimates for all 4 periods. These subjects were included in the individual and summary plasma APV concentration-time figures, the summaries of plasma APV and fosamprenavir concentration-time data, the summaries of plasma APV PK parameters, and the statistical analysis of the plasma APV PK data (comparison of treatment C to treatment A, treatment B to treatment A, and treatment D to treatment C). The demographics shown in table 2 are based on the PK summary population.

7.2 Pharmacokinetic Analysis

Fig 1 shows the mean plasma concentration-time curve of APV after oral administration of treatment A, B, C, and D.

Fig 1: Mean plasma concentration-time curve of APV after oral administration of treatment A, B, C, and D.



Treatment A: GW433908 oral film coated 2X700 mg tablets (fasted)
Treatment B: GW433908 oral film coated 2X700 mg tablets (with food)
Treatment C: 28 mL of the 50 mg/mL GW433908 oral suspension (fasted)
Treatment D: 28 mL of the 50 mg/mL GW433908 oral suspension (with food)

Table 4 shows the summary of pharmacokinetic results (geometric mean and 95 % CI) of APV after treatment A, B, C, and D.

Table 4: Summary of Pharmacokinetic Results of APV (geometric mean and 95 % CI) after treatments A, B, C, and D.

Parameter	Tablet Fasted Treatment A (N=32)	Tablet Fed Treatment B (N=32)	Suspension Fasted Treatment C (N=32)	Suspension Fed Treatment D (N=32)
AUC_{∞} (µg.h/mL)	16.52 (14.10-19.36)	15.93 (13.71-18.51)	15.86 (13.41-18.75)	11.40 (9.00-14.44)
AUC_{last} (µg.h/mL)	16.14 (13.76-18.92)	15.39 (13.24-17.88)	15.48 (13.09-18.31)	11.03 (8.71-13.98)
C_{max} (µg/mL)	4.03 (3.49-4.66)	4.44 (3.94-5.01)	4.62 (4.05-5.27)	2.50 (2.04-3.07)
$t_{½}$ (h)	4.02 (3.52- 4.60)	5.21 (4.56-5.96)	4.25 (3.63-4.97)	4.70 (4.09-5.40)
t_{max}[a] (h)	1.97 (0.73-3.00)	2.00 (0.72-5.02)	0.98 (0.48-2.50)	1.75 (0.47-5.02)
$AUC_{\%extrap}$	1.6 (1.2-2.2)	2.7 (2.0-3.5)	1.7 (1.3-2.3)	2.3 (1.7-3.0)
t_{lag}[a] (h)	0.00 (0.00-0.50)	0.25 (0.00-0.98)	0.00 (0.00-0.00)	0.00 (0.00-0.25)

Treatment A: Two GW433908 oral film-coated 700mg tablets administered fasted.
Treatment B: Two GW433908 oral film-coated 700mg tablets administered with food.
Treatment C: 28mL of 50mg/mL GW433908 oral suspension administered fasted.
Treatment D: 28mL of 50mg/mL GW433908 oral suspension administered with food.

a. t_{max} and t_{lag} are presented as median and range

The single-dose relative bioavailability of APV from GW433908 oral film-coated tablet and suspension formulations was evaluated by examining the ratio of the GLS means and the associated 90 % confidence interval of plasma APV pharmacokinetic parameters. Table 5 shows the statistical analysis of the pharmacokinetic parameters of APV observed after treatment A (tablet administered under fasting conditions) and treatment C (suspension administered under fasting conditions).

Table 5: Statistical analysis of the pharmacokinetic parameters of APV observed after treatment A (tablet administered under fasting conditions) and treatment C (suspension administered under fasting conditions) (C *vs* A).

Plasma APV PK Parameter	Geometric LS Mean		Ratio (90% CI) C/A
	Tablet Fasted (Treatment A)	Suspension Fasted (Treatment C)	
AUC_{∞} (µg.h/mL)	16.52	15.86	0.960 (0.843-1.093)
AUC_{last} (µg.h/mL)	16.14	15.48	0.959 (0.843-1.092)
C_{max} (µg/mL)	4.03	4.62	1.145 (1.011-1.297)
t_{max} (h)	1.83	1.16	0.633 (0.420-0.847)
$t_{½}$ (h)	4.02	4.25	1.055 (0.909-1.225)
Treatment A: Two GW433908 oral film-coated 700mg tablets administered fasted. Treatment C: 28mL of 50mg/mL GW433908 oral suspension administered fasted.			

a. t_{max} is presented as Geometric LS mean and ratio of the Geometric LS means.

Reviewer's Comment

The statistical analysis showed that the geometric mean and 90 % confidence interval for $AUC_{0-\infty}$ for the GLS mean ratio of tablet and suspension fell within the pre-specified 80-125 % interval. The GLS mean ratio for C_{max} was contained within the 80-125 % interval; however, the upper limit of the 90 % confidence interval for C_{max} (1.297) fell outside the pre-specified limits. This increase in C_{max} (and an earlier t_{max}) after administration of the suspension formulation can be explained on the basis of the faster absorption with the suspension formulation and is not expected to be of clinical concern.

7.3 Food Effect

Tablet

Table 6 shows the statistical analysis of the pharmacokinetic parameters of APV observed after treatment A (tablet administered under fasting conditions) and treatment B (tablet administered under fed conditions).

Table 6: Statistical analysis of the pharmacokinetic parameters of APV observed after treatment A (tablet administered under fasting conditions) and treatment B (tablet administered under fed conditions) (B *vs* A).

Plasma APV PK Parameter	Geometric LS Mean		Ratio (90% CI) B/A
	Tablet Fasted (Treatment A)	Tablet Fed (Treatment B)	
AUC_{∞} (µg.h/mL)	16.52	15.93	0.964 (0.846-1.098)
AUC_{last} (µg.h/mL)	16.14	15.38	0.953 (0.837-1.086)
C_{max} (µg/mL)	4.03	4.44	1.102 (0.973-1.247)
$t_{½}$ (h)	4.02	5.21	1.296 (1.116-1.505)
t_{max} (h)	1.83	2.42	1.326 (1.113-1.539)
Treatment A: Two GW433908 oral film-coated 700mg tablets administered fasted. Treatment B: Two GW433908 oral film-coated 700mg tablets administered with food.			

a. t_{max} is presented as Geometric LS mean and ratio of the Geometric LS means.

The results of the study indicated that the GLS mean ratio and the 90 % confidence interval for C_{max} and $AUC_{0-\infty}$ fell in the pre-specified confidence interval (80-125 %). Thus, there is no effect of food on the exposures from the tablet formulation.

Suspension

Table 7 shows the statistical analysis of the pharmacokinetic parameters of APV observed after treatment C (suspension administered under fasting conditions) and treatment B (suspension administered under fed conditions).

Table 7: Statistical analysis of the pharmacokinetic parameters of APV observed after treatment C (suspension administered under fasting conditions) and treatment D (suspension administered under fed conditions).

Plasma APV PK Parameter	Geometric LS Mean		Ratio (90% CI) D/C
	Suspension Fasted (Treatment C)	Suspension Fed (Treatment D)	
AUC_{∞}(µg.h/mL)	15.86	11.40	0.719 (0.631-0.819)
AUC_{last}(µg.h/mL)	15.48	11.03	0.713 (0.626-0.812)
C_{max} (µg/mL)	4.62	2.50	0.542 (0.479-0.614)
$t_{½}$ (h)	4.25	4.70	1.107 (0.954-1.286)
t_{max} (h)	1.16	1.99	1.720 (1.383-2.056)
Treatment C: 28mL of 50mg/mL GW433908 oral suspension administered fasted. Treatment D: 28mL of 50mg/mL GW433908 oral suspension administered with food.			

a. t_{max} is presented as Geometric LS mean and ratio of the Geometric LS means.

The results of the statistical analysis showed that administration of suspension under fasted and fed conditions **did not** provide equivalent APV systemic exposures. Administration of the fosamprenavir oral suspension with a standard high-fat breakfast decreased plasma APV $AUC_{0-\infty}$, AUC_{last}, and C_{max} values by 28.1 %, 28.7 %, and 45.8 %,

respectively, as compared to the GW433908 oral suspension formulation administered under fasting conditions.

Reviewer's Note Regarding Decrease in Exposures after Administration of the Suspension Formulation with Food

Due to the decrease in exposures of APV when the suspension formulation was administered with food, the package insert will indicate that the suspension formulation should always be taken under fasting conditions by ***adult*** *HIV-1 infected patients. The instructions for pediatric patients will be based on dosing instructions in pediatric PK, efficacy, and safety studies.*

8. Safety Assessments

Administration of single 1400 mg or 28mL of 50mg/mL suspension, each with and without food, was safe and well-tolerated. The adverse events reported in this study were similar to those previously reported for APV and FPV. The most commonly reported adverse events were headache (20 %). The most commonly reported drug-related adverse events were nausea (8 %) and diarrhea (5 %) (See details in Medical Officer's review).

9. Conclusion

- In the fasting state, the fosamprenavir oral suspension delivered an equivalent APV $AUC_{0-\infty}$ and a 14.5 % higher C_{max} (ratio of the GLS means: 1.145; 90% CI: 1.011- 1.297) as compared to the fosamprenavir oral tablet. This increase in C_{max} after administration of the suspension formulation is not expected to be of clinical concern.
- Administration of the fosamprenavir oral tablet with a high-fat breakfast resulted in equivalent plasma APV $AUC_{0-\infty}$ and C_{max} values as compared to the fosamprenavir oral tablet administered under fasting conditions.
- Administration of the GW433908 oral suspension formulation with a standard high-fat breakfast significantly decreased plasma APV $AUC_{0-\infty}$ and C_{max} values by 28.1 % and 45.8 %, respectively, as compared to the GW433908 oral suspension formulation administered under fasting conditions.

APV10024

1. Title

A Pivotal, Phase I, Open-Label, Randomized, Four Period, Two-Part, Crossover Study to Assess the Relative Bioavailability of the Fosamprenavir 50 mg/mL Oral Suspension and 700 mg Oral Film-Coated Tablet Formulations Following Administration of Single 1400 mg Doses and Following Administration of 1400 mg BID for 10 days in Healthy Adult Subjects.

2. Objectives

The objectives of this trial were:

- To assess the relative bioavailability of fosamprenavir (FPV) 50 mg/mL oral suspension and FPV 700 mg oral flim-coated tablet formulations.
- To compare steady-state plasma amprenavir (APV) PK following administration of FPV 50 mg/mL oral suspension and 700 mg oral film-coated tablet formulations.

3. Study Design

Eighty (80) subjects were planned to be enrolled in the Single Dose Part. If subjects withdrew from the study before starting Period 3, additional subjects were enrolled as replacement subjects to initiate dosing in 80 subjects in the Repeat Dose Part. Subjects were randomized to one of the four treatment sequences according to the randomization schedule shown in table 1.

Table 1: Randomization Scheme Used in Study APV10024

Treatment Sequence	N[1]		Single Dose Part		Repeat Dose Part		
			Period 1[2]	Period 2[2,3]	Period 3[2,3,5]	Period 4[5]	
1	20	Screen	A	B	C	D	Follow[4]-up
2	20		B	A	D	C	
3	20		A	B	D	C	
4	20		B	A	C	D	

A: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered fasted
B: Two FPV 700mg oral film-coated tablets administered fasted
C: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered twice daily (BID) for 10 days.
D: Two FPV 700mg oral film-coated tablets administered BID for 10 days.

1. Eighty (80) subjects were enrolled in the Single Dose Part. If subjects withdrew from the study before starting Period 3, additional subjects were enrolled as replacement subjects to initiate dosing in 80 subjects in the Repeat Dose Part.
2. Period 1 was followed by a 4-7-day washout period, Period 2 was not followed by a wash-out period, and Period 3 was followed by a 14-21 day washout period.
3. Period 2, Day 2 and Period 3, Day 1 occurred on the same calendar day.
4. Subjects returned to the study center for a follow-up visit within 14-21 days after completing the last treatment assessments or withdrawing from the study.
5. The last dose of FPV (either tablets or suspension) was administered on the morning of Day 10 for Period 3 and Period 4.

4. Drugs Used in the Trial

Table 2 shows the batch number of the tablet and suspension formulations used in the study. The tablet and suspension formulation used in the trial was identical to the approved (for tablet) and to-be-marketed (for the suspension) products respectively.

Table 2: Batch number of the tablet and suspension formulations used in the study.

Drug	Dose	Formulation	Batch Number
FPV	50 mg/mL	Oral Suspension	4F001
FPV	700 mg	Oral Film Coated Tablets	B130777

5. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples for the determination of APV concentrations in plasma during the single dose part were obtained pre-dose (within 5 minutes prior to dosing) and at the following time points after dosing: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours.

Blood samples for the determination of APV concentrations in plasma during the repeat dose part were obtained pre-dose (within 5 minutes prior to dosing) on Days 7, 8, 9, 10 and at the following time points after dosing on Day 10: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours.

Bioanalysis

Plasma samples were analyzed for APV by Worldwide Bioanalysis-Research Triangle Park (RTP), NC using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography with ⌜ ⌟ (HPLC/MS/MS) analysis. The calibration range for plasma amprenavir was ——— ——— The three quality control concentrations (QC) used in the bio-analysis were 35, 1000, and 8500 ng/mL. The lower limit of quantification (LLQ) for APV was 10 ng/mL using a 100 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 10,000 ng/mL. The intra/inter day precision (% CV) was ⌜ ⌟ The overall accuracy (% bias) for plasma amprenavir ranged from ⌜ ⌟ The long term freezer stability at -30 °C is at least 27 months. All samples were run within this time frame for both, aprenavir and fosamprenavir.

b(4)

Reviewer's Note:

The assay methodology is acceptable.

Pharmacokinetic Assessments

PK analysis of plasma APV concentration-time data was conducted using non-compartmental analysis using WinNonlin™ professional Version 4.1. The PK concentration population was comprised of subjects from whom a PK sample was obtained and analyzed. The PK parameter population was comprised of subjects in the PK concentration population who provided PK parameter estimates for any treatment. Similarly, the single dose and repeat-dose PK summary population was based on subjects who provided plasma APV PK parameter estimates for both periods 1 and 2 (single dose part) and periods 3 and 4 (repeat-dose part).

Statistical Analysis

Analysis of variance (ANOVA), using SAS (Version 8.2) Mixed Linear Models procedure, considering treatment sequence, period, and treatment as fixed effects and subject within sequence as a random effect was performed on log-transformed plasma APV PK parameters (except t_{max}) to assess the relative bioavailability of single 1400 mg doses of FPV 50mg/mL oral suspension and FPV 700mg oral film-coated tablet formulations and to assess equivalence at steady state following repeat dose administration (1400 mg BID) of the FPV 50 mg/mL oral suspension and FPV 700mg oral film-coated tablet formulations for 10 days. Data from Periods 1 and 2 with combined sequence AB and sequence BA were used to assess single dose bioequivalence and data from Periods 3 and 4 with combined sequence CD and DC were used to assess the steady-state equivalence of the two FPV formulations..

The PK dataset for the statistical analysis of the amprenavir pharmacokinetic parameters was based on the PK summary population. Plasma APV AUC_{∞}, AUC_{last}, and C_{max} were log-transformed prior to the primary analyses and treatment comparisons were expressed as ratios on the original scale.

6. Results

6.1 Subject Disposition

A total of 83 subjects were enrolled in the study and 69 subjects completed the study. Three of these 83 subjects were only enrolled during the Repeat Dose Part to replace the dropout subjects from single dose part of study. Eight subjects were withdrawn due to AEs, four subjects were lost to follow-up, and two subjects withdrew by not reporting to the site for the next period. Table 3 shows the summary of the subject disposition for APV10024.

Table 3: Summary of Subject Disposition for APV10024

Number of Subjects	Period 1	Period 2	Period 3	Period 4	Total
Planned, N	80	80	80	80	80
Entered[1], N	80	77	80	75	83
Completed, n (%)	77 (96%)	77 (100%)	75 (94%)	69 (92%)	69 (83%)
Total Withdrawn (any reason), n (%)	3 (4%)	0	5 (6%)	6 (8%)	14 (17%)
Withdrawn due to Adverse Events, n (%)	0	0	4 (80%)	4 (67%)	8 (57%)
Withdrawn due to lost to follow-up, n (%)	2 (67%)	0	0	2 (33%)	4 (29%)
Withdrawn due to subject decision to withdraw, n (%)[1]	1 (33%)	0	1 (20%)	0	2 (14%)

Source Data: Table 9.2

1. Three subjects were only enrolled in the repeat dose part of study.
2. Subject 24004 was withdrawn due to not reporting to the site for Period 4 check-in and Subject 24017 was withdrawn due to not reporting to the site for Period 2.

83 subjects received investigational product during the study (Safety Population). All 83 subjects underwent serial plasma PK sampling during at least one period (PK concentration Population). 77 subjects in Treatment A and 80 subjects in Treatment B provided PK parameters (Single Dose PK Parameter Population). *Two subjects (Subjects 24003 and 24005) were excluded due to vomiting within 4 hours of dosing following Period 2 dosing; therefore, PK parameters from Period 2 for these two subjects were excluded from the statistical analysis and summary of PK parameters.* A total of 75 subjects provided evaluable plasma APV PK parameter estimates for both Treatments A and B (Single Dose PK Summary Population). Seventy-seven (77) subjects in Treatment C and 78 subjects in Treatment D provided PK parameters (Repeat Dose PK Parameter Population); whereas, 71 subjects provided evaluable plasma APV PK parameter estimates for both Treatments C and D (Repeat Dose PK Summary Population).

Table 4: Demographics of Study APV 10024

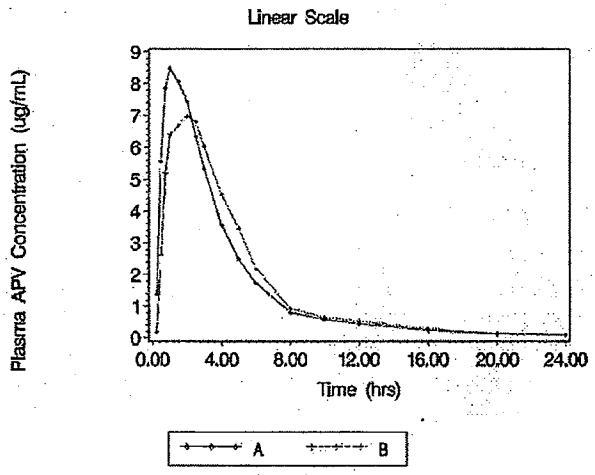
	Safety Population N=83	Single Dose PK Summary Population N=75	Repeat Dose PK Summary Population N=71
Age (yrs): Adults (18-55 years, inclusive):			
Mean (SD)	32.6 (8.50)	32.4 (8.58)	32.7 (8.56)
Median	32.0	32.0	33.0
Min. - Max.	20 - 51	20 – 51	21 - 51
Sex			
Female:	33 (40%)	29 (39%)	26 (37%)
Male:	50 (60%)	46 (61%)	45 (63%)
Ethnicity			
Hispanic or Latino:	68 (82%)	61 (81%)	56 (79%)
Not Hispanic or Latino:	15 (18%)	14 (19%)	15 (21%)
Race			
African American/African Heritage	5 (6%)	4 (5%)	5 (7%)
American Indian or Alaskan Native	1 (1%)	1 (1%)	1 (1%)
White - Arabic/North African Heritage	2 (2%)	2 (3%)	2 (3%)
White - White/Caucasian/European Heritage	36 (43%)	34 (45%)	30 (42%)
Not Reported	39 (47%)	34 (45%)	33 (46%)
Weight (kg)			
Mean, SD	70.49 (10.742)	70.76 (10.505)	71.26 (10.800)

6.2 Pharmacokinetic Analysis

Individual plasma APV concentrations were plotted against the actual time for the single- and repeat-dose part of the study. All pre-dose concentrations collected in the single dose phase (Periods 1 and 2) were not quantifiable (NQ), indicating no carry-over effect between dosing periods. There were no significant deviations in PK sampling times; all

samples were collected within 15 minutes of the scheduled time. Fig 1 shows the mean plasma concentration-time profile after single dose administration of suspension and tablet formulations under fasted conditions.

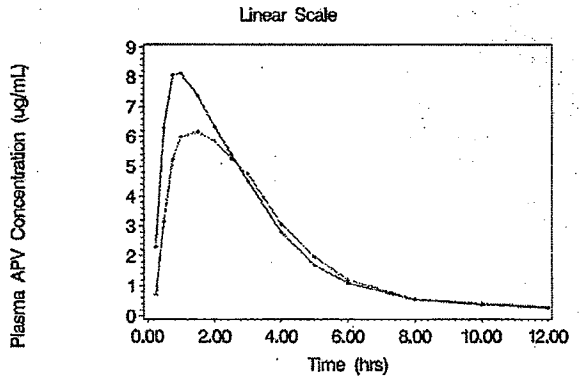
Fig 1: Mean plasma concentration-time profile after single dose administration of suspension and tablet formulations



A: 28 mL of FPV 50 mg/mL (1400 mg) oral suspension administered fasted
B: Two FPV 700 mg oral film coated tablets administered fasted.

Fig 2 shows the mean steady state plasma concentration-time profile after repeat dose administration of suspension and tablet formulations under fasted conditions.

Fig 2: Mean steady state plasma concentration-time profile after repeat dose administration of suspension and tablet formulations under fasted conditions.



C: 28 mL of FPV 50 mg/mL (1400 mg) oral suspension administered BID for 10 days
D: Two FPV 700 mg oral film coated tablets administered BID for 10 days.

Table 5 shows the summary of pharmacokinetic results {geometric mean (95 % CI)[% CV]} of APV after treatment A, B, C, and D.

Table 5: Summary of pharmacokinetic results {geometric mean (95 % CI) [% CV] of APV after treatment A, B, C, and D}

Plasma APV PK Parameter	Single Dose Part N=75		Repeat Dose Part N=71	
	Treatment A	Treatment B	Treatment C	Treatment D
AUC(0-∞) (µg.h/mL)	33.5[3] (29.9-37.6) [51]	35.1[4] (32.0-38.6) [42]	ND[2]	ND[2]
AUC(0-t) (µg.h/mL)	31.9 (28.3-35.9) [55]	34.0 (31.0-37.2) [41]	ND[2]	ND[2]
AUC(0-τ) (µg.h/mL)	ND[2]	ND[2]	26.4 (24.3-28.7) [36]	24.0 (22.0-26.1) [37]
Cmax (µg/mL)	8.74 (8.03-9.51) [38]	7.67 (7.09-8.29) [35]	8.25 (7.57-8.99) [37]	6.69 (6.12-7.30) [38]
Cτ (µg/mL)	ND[2]	ND[2]	0.401 (0.359-0.447) [49]	0.442 (0.394-0.496) [52]
tmax (h)[1]	1.00 (0.48-2.50)	2.00 (0.73-5.00)	0.98 (0.50-3.00)	1.50 (0.73-5.00)

Source Data: Table 10.3 and Table 10.8
Treatment A: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered fasted.
Treatment B: Two FPV 700mg oral film-coated tablets administered fasted.
Treatment C: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered BID for 10 days; fasted PK.
Treatment D: Two FPV 700mg oral film-coated tablets administered BID for 10 days; fasted PK.
1. tmax was presented as median (range)
2. ND: not determined
3. N=71
4. N=72

As compared to the tablet formulation, the higher C_{max} and the earlier t_{max} with the suspension formulation are consistent with the expected faster absorption of the suspension. The $AUC_{0-\infty}$ estimates were similar between treatments A and B and between treatments C and D. The results of plasma APV steady state assessments showed that for both treatments C and D, the slope estimates from the linear regressions of log-transformed plasma APV pre-dose concentrations collected on Days 8, 9, and 10 was close to zero and the 90 % CI included zero. Therefore, the amprenavir exposures on day 10 reflected steady state exposures.

Table 6 shows the treatment comparison for plasma APV PK parameters.

Table 6: Plasma APV PK Treatment Comparisons in APV10024

Plasma APV PK Parameter	Ratio of Geometric Least Squares Means (90% CI)	
	Single Dose Part Treatment A/Treatment B	Repeat Dose Part Treatment C/Treatment D
AUC(0-∞)	0.951 (0.879, 1.03)	ND[1]
AUC(0-t)	0.933 (0.857, 1.02)	ND[1]
AUC(0-τ)	ND[1]	1.10 (1.03, 1.17)
Cmax	1.13 (1.06, 1.20)	1.23 (1.16, 1.31)
Cτ	ND[1]	0.905 (0.848, 0.966)
tmax[2]	-0.75 (-1.00, -0.60)	-0.49 (-0.64, -0.25)

Source Data: Table 10.5 and Table 10.10
Treatment A: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered fasted.
Treatment B: Two FPV 700mg oral film-coated tablets administered fasted.
Treatment C: 28mL of the FPV 50mg/mL (1400mg) oral suspension administered BID for 10 days; fasted PK.
Treatment D: Two FPV 700mg oral film-coated tablets administered BID for 10 days; fasted PK.
1. ND: not determined
2. tmax: estimated median difference using Koch & Hauschke

Reviewer's Note Regarding Cross-Study Comparison of Results.

A comparison of exposure parameters observed in the two biopharmaceutics studies (APV10016 and APV10024) indicates that the exposure parameters (C_{max} and AUC) of the suspension and the tablet formulations observed in study APV10024 were approximately double the exposures observed in study APV10016. The applicant indicates that demographics and assay cannot explain these differences. Based on the reviewer's assessment, the primary differences between the two studies is the sample size between the two studies (n = 32 in APV10016 and N = 71 in APV10024) and the potential inter batch differences (if any) in the suspension and the tablet formulations used in the two studies. However, differences in sample size should primarily impact the confidence intervals and potential differences (if any) in batches are not expected to result in the magnitude of differences observed across the two studies. Therefore, the differences in exposure cannot be explained on the basis of the information currently available, however, since the studies were well controlled, the intra-study comparison of exposure parameters should still be valid.

7. Safety Assessments

No deaths or serious adverse events occurred during the study. The most commonly reported drug-related AEs in all four treatment groups were GI and nervous system disorders (nausea, diarrhea, headache, dizziness, and upper abdominal pain). Vomiting was noted more frequently in the oral suspension treatment groups compared to the tablet treatment groups in the single dose (3 % *vs.* 0 %) and repeat dose (13 % *vs.* 5 %) parts.

Eight subjects were withdrawn from the study due to AEs, which were considered drug-related by the investigator, during Treatments C and D: three subjects due to GI symptoms (2 during Treatment D and one during Treatment C), two subjects due to various types of rash during Treatment C, two subjects due to headache during Treatment C, and one subject due to pain in extremity during Treatment D (See details in Medical Officer's review).

8. Conclusion

- FPV 50 mg/mL oral suspension and 700 mg oral film-coated tablet formulations provided similar plasma APV exposures after single dose administration.
- Following repeat dose administration, the FPV 50 mg/mL oral suspension and 700 mg oral film-coated formulation delivered equivalent steady-state plasma APV $AUC_{0-\tau}$, however, the FPV 50 mg/mL oral suspension delivered a 23 % higher C_{max} as compared to the FPV 700 mg oral film-coated tablet formulation. This increase is C_{max} is not expected to be of clinical concern.

APV10017

1. Title

A Phase I, Parallel, Open-Label, Multicenter, Two-Week, Repeat-Dose Study Evaluating Plasma Amprenavir Pharmacokinetics in HIV-1 Infected Adult Subjects with Mild, Moderate, or Severe Hepatic Impairment Receiving Fosamprenavir +Ritonavir Compared to Matched Control Subjects with Normal Hepatic Function: Analyses of Mild and Moderate Hepatic Impairment.

2. Objectives

The primary objectives of this trial were:

- To compare plasma amprenavir pharmacokinetics in HIV infected subjects with mild hepatic impairment (as defined by a Child-Pugh score of 5-6) receiving fosamprenavir (FPV) 700 mg twice daily with a reduced frequency of ritonavir 100 mg once daily to subjects with normal hepatic function receiving FPV 700 mg BID + RTV 100 mg BID.
- To compare plasma APV PK in HIV-1 infected subjects with moderate hepatic impairment (as defined by a Child-Pugh score of 7-9) receiving FPV 300 mg BID with a reduced dosing frequency of RTV 100 mg QD to subjects with normal hepatic function receiving FPV 700 mg BID + RTV 100 mg BID.
- To compare plasma APV PK in HIV-1 infected subjects with severe hepatic impairment (as defined by a Child-Pugh score of 10-15) receiving FPV 300 mg BID with a reduced dosing frequency of RTV 100 mg QD to subjects with normal hepatic function receiving FPV 700 mg BID + RTV 100 mg BID.

3. Study Design

Phase I, parallel, open-label, two week repeat-dose study evaluating plasma APV and RTV PK in HIV-1 infected healthy subjects with mild, moderate and severe hepatic impairment compared to matched control subjects with normal hepatic function. Subjects with moderate hepatic impairment were randomized 1:1 to Group B or Group C (as described in table 1); recruitment into groups E and F was ongoing at the time of the report.

Table 1 shows the study design for study APV10017.

Table 1: Study Design for Study APV10017

Group	N	Hepatic Function Status	Dosing Regimen
A	10	Mild Hepatic Impairment[1]	FPV 700mg BID + RTV 100mg QD
B	10	Moderate Hepatic Impairment[2]	FPV 300mg BID + RTV 100mg QD
C	10	Moderate Hepatic Impairment[2]	FPV 700mg QD + RTV 100mg QD
D[4]	10	Normal Hepatic Function	FPV 700mg BID + RTV 100mg BID
E[6]	10	Severe Hepatic Impairment[3]	FPV 300mg BID + RTV 100mg QD
F[5,6]	10	Normal Hepatic Function	FPV 700mg BID + RTV 100mg BID

1. As determined by Child-Pugh score of 5-6
2. As determined by Child-Pugh score of 7-9
3. As determined by Child-Pugh score of 10-15
4. Subjects in Group D were enrolled to match subjects in Group B based on sex, weight (± 5 kg), and age (± 5 years).
5. Subjects in Group F are being enrolled to match subjects in Group E based on sex, weight (± 5 kg) and age (± 5 years).
6. Enrollment into Groups E and F is ongoing.

Reviewer's Note:

The study report for APV10017, submitted with the NDA, includes data from subjects with mild or moderate hepatic impairment (groups A-D). The information on subjects with severe hepatic impairment and their matched controls (for which enrollment is still ongoing) will be submitted in a subsequent report.

4. Rationale for Doses Evaluated in the Trial

Previously, the applicant conducted study PROB1008 to evaluate the plasma APV PK following administration of single doses of APV (delivered as AGENERASE™ [AGN], 600 mg) to HIV seronegative subjects with moderate or severe hepatic impairment compared to subjects with normal hepatic function. The results of the study showed that the plasma APV $AUC_{0-\infty}$ was approximately 150 % and 350 % higher in subjects with moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function.

The information related to dosing recommendation (700 mg BID un-boosted FPV) for subjects with mild and moderate hepatic impairment (Child-Pugh Score 5-8) in the currently approved Lexiva® package insert is based on a previously conducted study with amprenavir in subjects with mild, moderate, and severe hepatic impairment. Based on the amprenavir dose adjustments for subjects with mild, moderate, and severe hepatic impairment and the comparable plasma APV exposures achieved with equimolar doses of fosamprenavir and amprenavir, fosamprenavir dosing regimen of 525 mg BID would be appropriate in subjects with mild, moderate, and severe hepatic impairment. However, since only the 700 mg strength was available, 700 mg BID FPV (without ritonavir) was recommended to be used in subjects with mild and moderate hepatic impairment. There is currently no dosing recommendation for either un-boosted FPV for subjects with severe hepatic impairment (since the dose cannot be reduced with the currently approved

700 mg tablet formulation) or FPV/RTV in subjects with mild, moderate, or severe hepatic impairment.

Table 2 presents a summary of the dosing recommendations in the currently approved package insert of amprenavir and fosamprenavir in subjects with varying degrees of hepatic impairment.

Table 2: Summary of the dosing recommendations of amprenavir and fosamprenavir in subjects with varying degrees of hepatic impairment.

	Amprenavir		Fosamprenavir	
	Without Ritonavir	**With Ritonavir**	**Without Ritonavir**	**With Ritonavir**
Normal Hepatic Function	1200 mg BID	1200/200 mg QD or 600/100 mg BID	1400 mg BID	1400/200 mg QD or 700/100 mg BID
Mild Hepatic Impairment	450 mg BID	No labeling recommendation	700 mg BID	No labeling recommendation
Moderate Hepatic Impairment	450 mg BID	No labeling recommendation	700 mg BID	No labeling recommendation
Severe Hepatic Impairment	300 mg BID	No labeling recommendation	No labeling recommendation	No labeling recommendation

Dose Selection for Study

Mild Hepatic Impairment Group (FPV 700 mg BID + RTV 100 mg QD)

FPV 700 mg BID + RTV 100 mg BID is recommended in patients with normal hepatic function. As there are no data available for boosted APV in subjects with mild hepatic impairment and due to the fact that increases of 30 % - 60 % in plasma APV and RTV $AUC_{0-\tau}$ are likely in the mild hepatic impairment population (based on studies conducted with protease inhibitors such as Kaletra® and Crixivan®), the RTV dose was reduced by 50 % subjects with mild hepatic impairment.

Moderate Hepatic Impairment Group (FPV 300 mg BID + RTV 100 mg QD and FPV 700 mg QD+ RTV 100 mg QD)

Based upon the FPV and APV recommendations for reduced doses in subjects with moderate hepatic impairment, subjects with moderate impairment in APV10017 received repeat doses of FPV 300 mg BID + RTV 100 mg QD. An FPV 700 mg QD + RTV 100 mg QD regimen was also selected for study in subjects with moderate hepatic impairment in order to evaluate the FPV tablet formulation (administered with low dose ritonavir) in this population. The RTV 100 mg QD dose was selected because this is the lowest capsule strength available, the palatability of the RTV oral solution is poor, and plasma

RTV $AUC_{0-\tau}$ values are expected to be approximately 200 % higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.

*Severe Hepatic Impairment Group (FPV 300 mg BID + RTV 100 mg QD and FPV 700 mg QD+ RTV 100 mg QD)-**Currently Enrolling***

The FPV/RTV dosage regimen selected for administration to subjects with severe hepatic impairment in APV10017 was FPV 300mg BID with a reduced dosing frequency of RTV 100mg QD. The selection of this dosage regimen was based on the preliminary PK and safety data obtained for subjects with moderate hepatic impairment receiving FPV/RTV in APV10017 as well as on the PK data obtained in Study PROB1008.

5. Drugs Used in the Trial

Table 3 shows the batch number of the tablet and suspension formulations used in the study.

Table 3: Batch number of the tablet and suspension formulations used in the study

Drug	Dose/Form/Route	Batch Numbers
FPV	700mg oral film-coated tablets	B110573 B117130 B084053
FPV	Oral suspension Each mL of suspension contains 50mg of FPV, equivalent to 43.2mg/mL of APV	3K040 4E002 4F002 5B004
RTV	100mg oral soft gelatin capsules	342682E21 166902E22 10603VA

On days 1, 3, 7, 10, 13, and 14 (last dose), the doses were administered under the direct supervision of the study center staff; on all other days, doses were administered on an out-patient basis. The study drugs were to be administered at least 2 hours apart from a meal, but grape or apple juice was allowed to improve the palatability of the FPV oral suspension formulation.

6. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Subjects had a single pre-dose PK sample collected on the mornings of Days 3, 7, 10, 13, and 14 and serial post-dose PK samples collected over 12 hours (Group D) on Day 14 or 24 hours (Groups A, B, and C) on Day 14 and 15. Table 4 shows the pharmacokinetic sampling schedule followed.

Table 4: Pharmacokinetic Sampling Schedule in Study APV10017

Timing	Day	Time of Day	Planned Time Relative to Dosing (hours)
Pre-dose	3, 7, 10	morning	0 (trough)[1]
Pre-dose	13	morning	0 (trough)[1]
Pre-dose	14	morning	0 (trough)[1]
Post-dose	14	throughout day	0.25, 0.5, 0.75, 1, 1.5, 2[2], 2.5, 3, 4, 6, 8, 10, 12[2], 24[2,3]

1. One pre-dose (trough) PK sample was collected within 15 minutes prior to administration of the next dose.
2. Additional PK samples were collected at 2 hours (all subjects) and 12 hours (Groups A, B, D,) or 24 hours (Group C) after dosing on Day 14 for measurement of the extent of APV binding to human plasma proteins.
3. Collect 24-hour sample on Day 15 for Groups A, B, and C only.

The PK summary population included subjects who had plasma APV and RTV PK parameter estimates for a scheduled FPV/RTV regimen. Plasma APV and RTV PK parameters, except t_{max}, underwent natural log (ln) transformation prior to statistical analysis. Plasma APV and RTV C_τ values were the average of pre-dose concentrations collected at steady-state. Dose-normalized (DN) plasma APV C_{max}, C_τ, and $AUC_{(0-\tau)}$ were computed by normalizing to FPV 700 mg, where dose-normalized PK parameters for Group B were equal to PK parameter value X 700/300 and there was no change for Groups A, C, and D. Plasma APV and RTV AUC_{0-24} were equal to $AUC_{0-\tau}$ for QD regimens and were calculated as $AUC_{0-\tau}$ X 2 for BID regimens. The percent unbound APV at a specific time was calculated as plasma unbound APV concentration at that time/plasma total APV concentration at the same time-point X 100, e.g. % C2h_unbound = (C2h_unbound/C2h_total plasma) X 100%.

Bioanalysis

For each analyte, QC samples, prepared at three different analyte concentrations (for APV, FPV, and RTV) or four different analyte concentrations (for unbound APV) and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards.

Plasma samples were analyzed for APV and FPV by Worldwide Bioanalysis, DMPK, GSK, RTP using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography (HPLC) with ⌜ ⌟ (MS/MS) analysis. The calibration range for plasma amprenavir was ⌜ ⌟ and the three quality control concentrations were 35, 800, and 4000 ng/mL. The lower limit of quantification (LLQ) for APV was 10 ng/mL using a 100 µL aliquot of human plasma with a higher limit of quantification (HLQ) of 5000ng/mL; the LLQ for FPV was 5ng/mL and HLQ was 1000ng/mL. The intra/inter day precision in plasma amprenavir was ——— ——— The overall accuracy (% bias) ranged from ⌜ ⌟ The long term freezer stability for both fosamprenavir and amprenavir at -30 °C was at least 27 months. All samples were run within this time frame for fosamprenavir and amprenavir.

b(4)

Protein-free plasma ultrafiltrate samples were analyzed for APV by [redacted] using a validated analytical method based on [redacted] followed by HPLC/MS/MS analysis. The calibration range for plasma amprenavir in the ultra filtrate was [redacted] and the three quality control concentrations were 1.5, 425, and 750 ng/mL. The LLQ for APV was 0.5 ng/mL using a 100 µL aliquot of human protein-free plasma ultrafiltrate with a HLQ of 1000ng/mL. The intra/inter day precision in plasma amprenavir was [redacted] The overall accuracy (% bias) ranged from [redacted] The long term freezer stability for both fosamprenavir and amprenavir at -20 °C was at least 486 days. All samples were run within this time frame for fosamprenavir and amprenavir. b(4)

Reviewer's Note:

The assay methodology is acceptable. The applicant acknowledges that since the trial is ongoing, some of the assay related information (e.g. intra/inter day precision, overall accuracy) may change upon completion of the studies.

Pharmacokinetic Assessments

PK analysis of plasma APV concentration-time data was conducted using [redacted] The actual plasma PK sampling collection times were used in the PK analysis. b(4)

Statistical Analysis

Descriptive statistics of plasma APV and RTV concentration data at each planned relative time were presented by group. Mean and median steady-state plasma APV and RTV concentration-time profiles were displayed by group on both semi-logarithmic and linear scales. Plasma APV PK parameters were compared between each hepatic impairment group and subjects with normal hepatic function by ANOVA, considering group as a fixed effect. The ratio of geometric least square (GLS) means and associated 90 % CI for the group comparisons was presented. Achievement of steady state plasma APV and RTV concentrations was assessed by calculating the 90% CI of the slope of the linear regression of pre-dose concentrations from Days 10, 13, and 14 versus Day for each group. The same analysis was performed with Days 7, 10, 13, and 14, and with Days 13 and 14.

7. Results

7.1 Subject Disposition

A total of 43 subjects were enrolled in the study: 13 were enrolled in Group A (mild hepatic impairment), 20 were enrolled in Groups B and C (moderate hepatic impairment), and 10 were enrolled in Group D (normal hepatic impairment). One of the 10 subjects in Group C had mild hepatic impairment based on Child-Pugh score, but was enrolled in Group C in error. Two subjects in the mild hepatic impairment cohort withdrew from the

study; subject 6 was withdrawn due to an AE (gastritis) after one day of dosing with FPV/RTV and Subject 43 decided to withdraw from the study after eight days of dosing.

42 subjects were included in the PK Concentration Population (PK concentration population comprised of subjects who underwent PK sampling), 41 subjects were included in the PK Parameter Population (PK parameter population consisted of subjects who had plasma amprenavir **or** ritonavir PK parameter estimates) and 38 subjects were included in the PK Summary Population (PK summary population consisted of subjects who had plasma amprenavir **and** ritonavir PK parameter estimates). Table 5 shows the demographic characteristics in APV10017.

Table 5: Summary of Subject Disposition for APV10017

Demographic Characteristic	Mild HI FPV BID/ RTV QD (Group A) N=13	Moderate HI FPV BID/ RTV QD (Group B) N=10	Moderate HI FPV QD/ RTV QD (Group C) N=10	Normal Hepatic Function FPV/RTV BID (Group D) N=10	Total N=43
Age					
Mean (SD)	42.2 (4.69)	44.0 (3.46)	43.7 (5.31)	43.4 (4.40)	43.3 (4.42)
Median	43.0	43.5	42.5	45.0	44.0
Range	34, 50	39, 49	36, 54	34, 49	34, 54
Sex, n (%)					
Female:	1 (8)	2 (20)	2 (20)	2 (20)	7 (16)
Male:	12 (92)	8 (80)	8 (80)	8 (80)	36 (84)
Ethnicity, n (%)					
Hispanic or Latino:	0	1 (10)	4 (40)	2 (20)	7 (16)
Not Hispanic or Latino:	13 (100)	9 (90)	6 (60)	8 (80)	36 (83)
Race, n (%)					
African American/African Heritage:	0	0	1 (10)	1 (10)	2 (5)
White- White/Caucasian/ European Heritage:	13 (100)	10 (100)	9 (90)	9 (90)	41 (95)
BMI (kg/m²)					
Mean (SD)	23.62 (3.43)	24.25 (4.40)	24.81 (3.35)	25.89 (4.66)	24.57 (3.91)
Weight (kg)					
Mean (SD)	71 (13.9)	69 (13.0)	72 (10.9)	71 (12.2)	71 (12.2)

Source Data: Table 9.5 and Table 9.7.
HI = hepatic impairment

7.2 Pharmacokinetic Analysis

FPV concentrations were low in all treatment groups, and FPV concentrations in all samples after the 4-hour post-dose sampling time were not quantifiable.

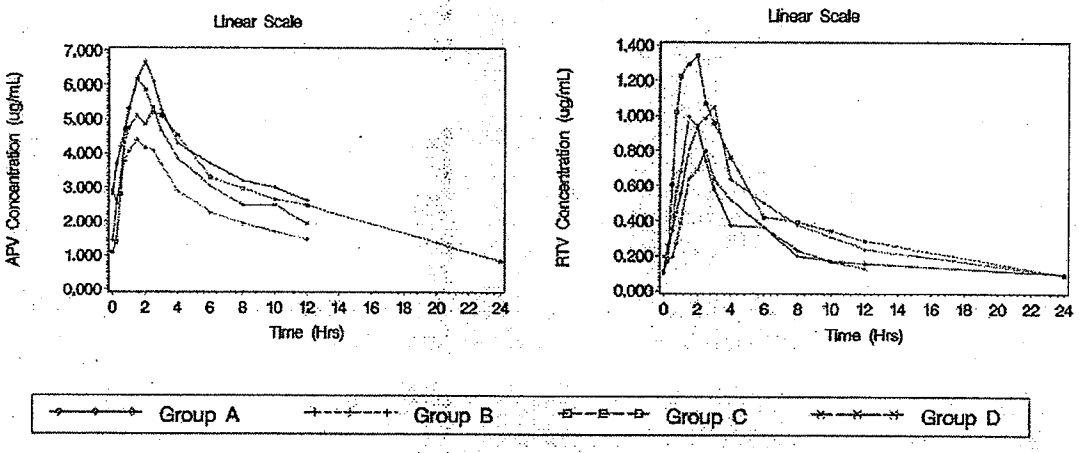
One subject in Group C (subject 182) had undetectable pre-dose plasma APV and RTV concentrations at Day 7, suggesting non-adherence during that time of the study. For a number of subjects, pre-dose samples on days 3, 7, 10, and 13 were collected after the dosing, therefore, the samples collected on these days were excluded from the C_t calculations. The 2-hour plasma unbound APV concentrations were collected at approximately 5 hours post dose for Subject 27 (Group B) and Subject 94 (Group D). In addition, the 12-hour plasma unbound APV concentration was collected at 8 hours post dose for Subject 179 (Group D). These samples were excluded from the summary and statistical analysis of 2- hour and Ct unbound concentrations and % unbound. Further,

there were some subjects with missing Day 14 FPV and RTV dosing date/time information, therefore, scheduled time was used in the PK analysis.

Steady state plasma APV and RTV concentrations were achieved by Day 14 for all treatment groups. For Groups B, C, and D, the slope estimates from the linear regressions of log-transformed plasma APV and RTV pre-dose concentrations collected on Days 7, 10, 13, and 14 were close to zero and the 90% CI included zero

Fig 1 shows the mean steady-state plasma amprenavir concentrations for the four treatment groups.

Fig 1: Mean steady-state plasma amprenavir A) and ritonavir (B) concentrations for the four treatment groups.



Group A = Mild Hepatic Impairment FPV 700mg BID + RTV 100mg QD
Group B = Moderate Hepatic Impairment FPV 300mg BID + RTV 100mg QD
Group C = Moderate Hepatic Impairment FPV 700mg QD + RTV 100mg QD
Group D = Normal Hepatic Function FPV 700mg BID + RTV 100mg BID

Mild Hepatic Impairment

Table 4 shows the summary and statistical comparison of selected pharmacokinetic plasma APV pharmacokinetic parameters for mild hepatic impairment and normal hepatic function groups in APV10017.

Table 4: Summary and statistical comparison of selected pharmacokinetic plasma APV pharmacokinetic parameters for mild hepatic impairment and normal hepatic function groups in APV10017.

Plasma APV PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	Mild HI (Group A) N=10	Normal Hepatic Function (Group D) N=10	Mild HI vs Normal Hepatic Function
AUC(0-τ) (µg.h/mL)	46.6 [39.0, 55.5] (25)	38.1 [31.6, 46.0] (27)	1.22 [0.94, 1.59]
Cmax (µg/mL)	7.04 [5.72, 8.66] (30)	6.00 [4.97, 7.25] (27)	1.17 [0.90, 1.53]
Cτ (µg/mL)	2.38 [1.80, 3.15] (40)	2.62 [2.14, 3.21] (29)	0.91 [0.63, 1.32]
CL/F (mL/min)	215 [180, 256] (25)	262 [217, 316] (27)	0.82 [0.63, 1.07]
t1/2 (h)	7.89[1] [5.83, 10.7] (38)	6.44[1] [4.99, 8.32] (31)	1.23 [0.89, 1.69]

HI: Hepatic Impairment
Mild HI: Hepatic Fibrosis + Child Pugh Score of 5-6
Group A: FPV 700 mg BID + RTV 100 mg QD X 14 days
Group D: FPV 700 mg BID + RTV 100 mg QD X 14 days

Subjects with mild hepatic impairment receiving standard doses of FPV 700mg BID (administered as the FPV tablet) in combination with a reduced dosing frequency of RTV 100 mg QD had approximately 17-23 % higher plasma APV C_{max}, $AUC_{0-\tau}$, and $t_{1/2}$ values, 18 % lower CL/F, and similar C_τ values compared to subjects with normal hepatic function receiving FPV/RTV 700/100mg BID.

Unbound Amprenavir

Subjects with mild hepatic impairment receiving standard doses of FPV 700 mg BID (administered as the FPV tablet) in combination with a reduced dosing frequency of RTV 100 mg QD had higher plasma unbound APV concentrations and higher % unbound APV compared to subjects with normal hepatic function.

Table 6 shows the summary and statistical comparison of plasma unbound APV concentrations for mild hepatic impairment and normal hepatic function groups.

Table 6: Summary and statistical comparisons of plasma unbound APV concentrations for mild hepatic impairment and normal hepatic function groups in APV10017.

Plasma Unbound APV Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	Mild HI (Group A) N=10	Normal Hepatic Function (Group D) N=9	Mild HI vs Normal Hepatic Function
2-h concentration (µg/mL)	0.56 [0.42, 0.75] (41)	0.35 [0.30, 0.41] (21)	ND
C_τ (µg/mL)	0.26 [0.19, 0.36] (42)	0.12 [0.10, 0.15] (24)	ND
2-hour % unbound	8.92 [7.68, 10.4] (21)	7.53 [6.10, 9.29] (28)	1.18 [0.94, 1.50]
C_τ % unbound	10.9 [8.88, 13.3] (25)	6.16 [4.52, 8.38] (42)	1.77 [1.37, 2.27]

HI: Hepatic Impairment
Mild HI: Hepatic Fibrosis + Child Pugh Score of 5-6
Group A: FPV 700 mg BID + RTV 100 mg QD X 14 days
Group D: FPV 700 mg BID + RTV 100 mg QD X 14 days

Reviewer's Note:

The plasma AAG concentrations for subjects with mild and moderate hepatic impairment were approximately half of the AAG concentrations for subjects with normal hepatic function. Therefore, the unbound fraction and unbound concentrations were expected to be higher in subjects with hepatic impairment.

Moderate Hepatic Impairment

When plasma APV PK was normalized to a 700 mg dose, moderate hepatic impairment significantly increased plasma total APV dose normalized $AUC_{0-\tau}$ by 51-70 % following administration of FPV/RTV. However, when the PK parameters were compared without dose-normalization, the two-tested FPV/RTV regimens delivered lower plasma total APV exposures compared to subjects with normal hepatic function receiving a standard FPV/RTV 700/100 mg BID regimen. Table 7 shows the summary and statistical comparisons of selected plasma APV pharmacokinetic parameters for moderate hepatic impairment and normal hepatic function groups.

Table 7: Summary and statistical comparisons of selected plasma APV pharmacokinetic parameters for moderate hepatic impairment and normal hepatic function groups.

Plasma APV PK Parameter	Geometric Mean (95% CI) [CVb%] Moderate HI FPV BID/ RTV QD (Group B) N=10	Moderate HI FPV QD/ RTV QD (Group C) N=8	Normal Hepatic Function FPV BID/ RTV BID (Group D) N=10	GLS Mean Ratio (90% CI) Moderate HI vs Normal Hepatic Function Group B vs Group D	Group C vs Group D
Dose Normalized					
DN-AUC(0-τ) (µg.h/mL)	64.8 [46.5, 90.4] (49)	57.8 [42.1, 79.3] (39)	38.1 [31.6, 46.0] (27)	1.70 [1.31, 2.21]	1.51 [1.15, 2.00]
DN-Cmax (µg/mL)	10.2 [7.18, 14.5] (52)	6.68 [5.14, 8.70] (32)	6.00 [4.97, 7.25] (27)	1.70 [1.30, 2.22]	1.11 [0.84, 1.48]
DN-Cτ (µg/mL)	2.63 [1.73, 3.99] (64)	0.93 [0.53, 1.62] (75)	2.62 [2.14, 3.21] (29)	1.00 [0.69, 1.45]	0.35 [0.24, 0.53]
Observed					
AUC(0-τ) (µg.h/mL)	27.8 [19.9, 38.7] (49)	57.8 [42.1, 79.3] (39)	38.1 [31.6, 46.0] (27)	0.73 [0.56, 0.95]	1.51 [1.15, 2.00]
Cavg (µg/mL)	2.32 [1.66, 3.23] (49)	2.41 [1.75, 3.30] (39)	3.18 [2.64, 3.83] (27)	0.73 [0.56, 0.95]	0.76 [0.57, 1.00]
Cmax (µg/mL)	4.38 [3.08, 6.22] (52)	6.68 [5.14, 8.70] (32)	6.00 [4.97, 7.25] (27)	0.73 [0.56, 0.95]	1.11 [0.84, 1.48]
Cτ (µg/mL)	1.13 [0.74, 1.71] (64)	0.93 [0.53, 1.62] (75)	2.62 [2.14, 3.21] (29)	0.43 [0.30, 0.62]	0.35 [0.24, 0.53]
CL/F (mL/min)	154 [111, 215] (49)	173 [126, 238] (39)	262 [217, 316] (27)	0.59 [0.45, 0.76]	0.66 [0.50, 0.87]
t1/2 (h)	6.78[1] [4.60, 10.0] (49)	7.96 [5.93, 10.7] (36)	6.44[1] [4.99, 8.32] (31)	1.05 [0.76, 1.45]	1.23 [0.90, 1.70]

HI: Hepatic Impairment
Moderate HI: Hepatic Fibrosis +Child Pugh Score of 7-9
Group B: FPV 300 mg BID + RTV 100 mg QD X 14 days
Group C: FPV 700 mg QD + RTV 100 mg QD X 14 days
Group D: FPV 700 mg BID + RTV 100 mg BID X 14 days

The similarity in CL/F and dose normalized C_{avg} between the two groups suggests that the PK is expected to be similar for both dosing regimens.

Based on this data, the applicant suggests that FPV 450 mg BID + RTV 100 mg QD is predicted to deliver average $AUC_{0-\tau}$ (41.7 µg*hr/mL) similar to subjects with normal hepatic function receiving the standard FPV/RTV 700 mg/100 mg BID regimen.

Reviewer's Note

*FPV 450 mg BID + RTV 100 mg QD (proposed by the applicant) is predicted to deliver average $AUC_{0-\tau}$ (41.7 μg*hr/mL) similar to subjects with normal hepatic function receiving the standard FPV/RTV 700 mg/100 mg BID regimen. The predicted steady state total (bound + unbound) C_τ levels (~1.7 μg/mL) after administration of 450 mg BID + RTV 100 mg QD are expected to be lower than the total (bound + unbound) C_τ levels (2.62 μg/mL) after administration of 700 mg BID + 100 mg BID, however, the unbound plasma APV C_τ is expected to be ~70 % higher after administration of 450 mg BID + 100 mg QD (due to increase in the unbound fraction in subjects with hepatic impairment). Therefore, the antiviral efficacy (which is primarily governed by the unbound concentrations of the drug) is not expected to be lower in subjects with moderate hepatic impairment after administration of FPV 450 mg BID + 100 mg RTV QD as compared to subjects with normal hepatic function after administration of 700 mg BID + RTV 100 mg BID.*

Unbound Amprenavir

Subjects with moderate hepatic impairment receiving standard doses of FPV 700mg BID (administered as the FPV tablet) in combination with a reduced dosing frequency of RTV 100mg QD had higher plasma unbound APV concentrations and higher % unbound APV compared to subjects with normal hepatic function. Table 8 shows the summary and statistical comparisons of plasma unbound APV concentrations for mild hepatic impairment and normal hepatic function groups.

Table 8: Summary and statistical comparisons of plasma unbound APV concentrations for moderate hepatic impairment and normal hepatic function groups.

	Geometric Mean [95% CI] (CVb%)			GLS Mean Ratio [90% CI]	
	Moderate HI		Normal Hepatic Function	Moderate HI vs Normal Hepatic Function	
Plasma Unbound APV Parameter	FPV BID/ RTV QD (Group B) N=9	FPV QD/ RTV QD (Group C) N=7	FPV BID/ RTV BID (Group D) N=9	Group B vs Group D	Group C vs Group D
2-h concentration (μg/mL)	0.35 [0.20, 0.61] (82)	0.67 [0.56, 0.80] (20)	0.35 [0.30, 0.41] (21)	ND	ND
C_τ (μg/mL)	0.15 [0.08, 0.26] (88)	0.07[1] [0.04, 0.14] (69)	0.12 [0.10, 0.15] (24)	ND	ND
2-hour % unbound	10.1 [7.49, 13.5] (40)	11.8 [8.81, 15.8] (32)	7.53 [6.10, 9.29] (28)	1.33 [1.05, 1.69]	1.57 [1.21, 2.02]
C_τ % unbound	12.5 [9.98, 15.5] (29)	9.26[1] [7.37, 11.6] (22)	6.16 [4.52, 8.38] (42)	2.02 [1.58, 2.58]	1.50 [1.15, 1.98]

HI: Hepatic Impairment
Moderate HI: Hepatic Fibrosis +Child Pugh Score of 7-9
Group B: FPV 300 mg BID + RTV 100 mg QD X 14 days
Group C: FPV 700 mg QD + RTV 100 mg QD X 14 days
Group D: FPV 700 mg BID + RTV 100 mg BID X 14 days

8. Conclusion

- For subjects with **mild hepatic impairment**, a dosing regimen of FPV 700mg BID with a reduced dosing frequency of RTV 100mg QD showed higher plasma APV C_{max} (17 %), slightly higher plasma APV $AUC_{0-\tau}$ (22 %), and similar C_{τ} values compared to subjects with normal hepatic function receiving the standard FPV/RTV 700mg/100mg BID regimen. **The proposed dose is acceptable.**
- For subjects with **moderate hepatic impairment**, a dosage regimen of 450mg BID with a reduced dosing frequency of RTV 100mg QD is predicted to deliver plasma APV $AUC_{0-\tau}$ values similar to values observed for subjects with normal hepatic function receiving the standard FPV/RTV 700/100mg BID regimen. **The proposed dose is acceptable.**

APV20003

1. Title

A 48 Week, Phase II, Open-Label, Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Fosamprenavir/Ritonavir QD and Fosamprenavir/Ritonvir BID when Administered to HIV-1 Infected, Antiretroviral Naïve and Experienced, Pediatric Subjects 2 to 18 Years Old.

2. Objectives

The clinical pharmacology related objectives of this trial were to characterize plasma APV PK following administration of FPV/RTV once daily and twice daily to pediatric subjects 2 to ≤ 18 years of age.

3. Study Design

APV20003 was an international, 48-week, Phase II, open-label, multi-cohort, multicenter study conducted in 69 HIV-1 infected, pediatric subjects 2 to ≤ 18 years old. Table 1 shows the planned number of subjects by cohort for the study.

Table 1: Planned Number of Subjects by Cohort for APV20003

Cohort[1]	Age	ART-naïve[2] and ART-experienced[3] FPV/RTV QD
1	2 to <6 years	16
2	6 to <12 years	12
3	12 to 18 years	10
4[4,5]	2 to 18 years	24

1. Cohorts 1, 2 and 3 enrolled in parallel. Subjects in these cohorts had PK trough sampling on Weeks 8, 12, 24 and 48 and a PK profile on Week 4.
2. ART-naïve subjects received ABC/3TC.
3. GlaxoSmithKline provided **optional** ABC and/or 3TC to ART-experienced subjects whose HIV-1 genotype showed susceptibility to ABC and/or 3TC.
4. Subjects were permitted to enroll in Cohort 4 when enrolment of the appropriate number of similarly aged subjects in Cohorts 1, 2 or 3 was complete.
5. Subjects in Cohort 4 had PK trough sampling on Weeks 4, 8, 12, 24 and 48.

ART-naïve or ART-experienced pediatric subjects, 2 to ≤ 18 years of age (Cohorts 1, 2 and 3), began multiple dosing with FPV 30 mg/kg + RTV 6 mg/kg QD on Day 1. A Week 4 PK profile over 24 hours (at 0, 1, 2, 4, 8, 12, and 24 hours post dosing) and additional PK trough sampling at Weeks 8, 12, 24 and 48 was characterized. The plasma PK samples collected at Week 4 were analyzed for APV concentrations to confirm if the target plasma APV exposure was achieved. Based on the Week 4 plasma APV PK data from at least 6 subjects who receive the FPV oral suspension, the dose of the FPV oral suspension was to be adjusted for all subjects in the cohort. If dose adjustment was necessary, all subsequently enrolled subjects in the cohort would receive the newly recommended dose.

Protocol amendment # 4 was implemented on August 20, 2003 after 54 subjects were enrolled in the trial. The following adult data supported the modification:

1) **Switching of subjects from a QD to a BID regimen:** The applicant completed Week 48 data analysis of study APV30003 which enrolled 360 PI-experienced, HIV-1 infected adults with evidence of virologic failure. In this study, FPV/RTV BID and FPV/RTV QD were compared to LPV/RTV BID. Based on the applicant analysis, FPV/RTV BID arm had similar efficacy to the LPV/RTV BID arm while the observed antiviral response rates for the FPV/RTV QD arm were lower. Therefore, an option was provided for management of subjects who were PI-experienced at Baseline/Day 1 to either maintain their current FPV/RTV QD regimen or to switch to a FPV/RTV BID regimen. This resulted in the creation of a subset of "switch subjects" who switched their FPV/RTV QD to the FPV/RTV BID regimen at any time within the study, at the investigators' discretion.

2) **Increase in dose for subjects switching from a QD regimen to a BID regimen:** Based on preliminary PK data from APV20003, a 33 % dose increase was recommended for all Cohort 1 subjects who were PI-experienced at Baseline/Day 1 and switching to a FPV/RTV BID regimen. These "switch subjects" received FPV 20 mg/kg BID in combination with RTV 4 mg/kg BID. However, once these subjects reached 6 years of age, they underwent a dose adjustment to 15 mg/kg FPV BID in combination with RTV 3 mg/kg BID (the FPV/RTV BID dosing regimen being administered to all "switch subjects" > 6 to 18 years of age).

4. Selection of Study Population

Sixty-nine HIV-1 infected, ART-naïve and experienced pediatric subjects 2 to ≤ 18 years of age, with screening plasma HIV-1 RNA ≥ 400 copies/mL and who met all eligibility criteria were enrolled into this study.

ART-naïve subjects were defined as having ≤ 4 weeks (28 days) therapy with any NRTI(s), no previous therapy with any non-nucleoside reverse transcriptase inhibitor(s) [NNRTI(s)] and ≤ 1 week therapy with an HIV PI. ART-experienced subjects were defined as having had greater than 4 weeks (28 days) therapy with any NRTI(s); prior therapy (of any length) with any NNRTI(s) and/or a PI was allowed.

5. Drugs Used in the Trial

FPV was administered as either oral 700mg tablets (600mg APV molar equivalents) or 50mg/mL oral suspension (43.2mg/mL APV molar equivalents). Table 2 shows the FPV formulations used in the study.

Table 2: Batch number of FPV Formulations Used in the Study.

Drug Name		Batch Numbers
Fosamprenavir tablets	700 mg	B048577, B067230, B048577, B059742, B066070, B084190, B076989, B076989, B121918
Fosamprenavir solution	50 mg/mL	1L723, 2A703, 1L7223, 2A704, 3G039, 3K040, 4B001

RTV was given as either an 80mg/mL oral solution (batch numbers: 18723AW21, 21802AW21; 23840AW21) or 100mg capsules (batch numbers: 039852E21; 075392E21; 932942E21; 82855E21; 83398VA; 84526VA; 88673VA; 95118VA; 03719VA; 10359VA; 95118VA; 10359VA; 17613VA). The tablet and suspension formulation used in the trial was identical to the approved (for tablet) and to-be-marketed (for the suspension) products respectively.

6. Dosage and Administration

Subjects could only receive one FPV formulation at any given time (i.e., subjects could not receive one FPV 700mg tablet and FPV suspension simultaneously to achieve adequate FPV intake). Similarly, subjects could only receive one RTV formulation at any given time.

FPV/RTV QD

FPV 700 mg tablets were available to subjects who were at least 12 years of age, weighed ≥ 50kg and who were able to swallow whole tablets, at the discretion of the investigator. These subjects were to receive an adult dosage regimen of FPV 1400mg QD in combination with RTV 200mg QD. RTV 100 mg capsules were made available to subjects who weigh ≥ 33kg and who were able to swallow whole capsules, at the discretion of the investigator.

Subjects taking the FPV oral suspension would receive FPV 30 mg/kg (up to a maximum daily dose of 1800 mg QD) in combination with RTV 6 mg/kg QD (up to a maximum daily dose of 200 mg). The FPV oral suspension doses (30 mg/kg up to a maximum of 1800 mg) was higher than the previously approved FPV doses to account for the impact of food on the systemic exposures of the suspension formulation (food reduces the exposure from the suspension formulation).

FPV/RTV BID (for Subjects Switching from FPV/RTV QD)

As per the protocol modification, subjects were allowed to switch from a FPV/RTV QD regimen to a FPV/RTV BID regimen since 48-Week analysis of trial APV 30003 (conducted by the applicant) showed that the antiviral response rates were lower in the QD arm as compared to the BID arm.

Subjects who were PI-experienced at Baseline/Day 1 and receiving FPV tablets QD in combination with RTV QD who switched to the FPV/RTV BID regimen were to receive 700 mg FPV BID in combination with RTV 100mg BID.

Cohort 1 subjects who were PI-experienced at Baseline/Day 1 and received the FPV oral suspension QD in combination with RTV QD and who switched to FPV /RTV BID were to receive a starting dose FPV 20 mg/kg BID (up to a maximum daily dose of 1800 mg) in combination with RTV 4 mg/kg BID.

Cohorts 2, 3 and 4 subjects who were PI-experienced at Baseline/Day 1 and received the FPV oral suspension QD in combination with RTV QD who switched to a FPV/RTV BID regimen would receive a starting dose FPV 15 mg/kg BID (up to a maximum daily dose of 1800 mg) in combination with RTV 3 mg/kg BID.

Study Drug Administration

The FPV suspension was to be shaken as per the label instructions prior to measuring. Both the FPV oral suspension and the RTV oral solution were to be measured and administered *via* separate dosing syringes. Administration via dosing cups was not allowed as residual FPV oral suspension and RTV oral solution could remain in the cups.

The FPV oral suspension and RTV oral solution were recommended to be administered with food to accommodate the frequent eating schedule of children, to enhance the adherence through taste masking with food, and to improve tolerability.

7. Dose Rationale

The selection of the FPV/RTV 30/6mg/kg QD regimen for evaluation in pediatric subjects between the ages of 2 to 18 years of age was originally based on the following information and considerations:

- The approved un-boosted AGENERASE (APV) capsule dosage regimen in children 4 to 16 years old (13 to 16 year olds weighing less than 50 kg) is 20 mg/kg BID.
- Equimolar doses of FPV and APV deliver comparable plasma APV exposures, therefore, an un-boosted FPV 23 mg/kg BID dosage regimen is expected to deliver plasma APV exposure comparable to the equimolar un-boosted APV 20 mg/kg BID regimen.
- Administration of FPV oral suspension formulation with food reduced plasma APV $AUC_{0-\infty}$ by 28 %. The FPV oral suspension was recommended to be administered with food to children in order to accommodate the frequent eating schedule of children, to enhance adherence through taste masking with food, and to improve the tolerability of RTV. Therefore, the FPV dose was adjusted for the observed food effect by increasing the un-boosted FPV dose from 23 mg/kg BID to 30 mg/kg BID.

- The FPV QD dose administered to adults with RTV (FPV/RTV 1400/200mg QD) is half the total daily un-boosted FPV dose (FPV 1400 mg BID), so a FPV 30 mg/kg QD dose was selected to be administered in combination with RTV in children 2 to 18 years of age in this study.
- As the RTV dose co-administered with FPV in adults is 1/6 of the standard dose, the RTV 6 mg/kg dose was selected for co-administration with FPV 30 mg/kg QD in children 2 to 18 years of age because this dose was 1/6 of the standard dose recommended for children.

Based on the results of the pivotal adult clinical trial APV30003 (where both FPV/RTV QD and BID were evaluated), the protocol was amended to allow subjects to switch from a FPV/RTV QD regimen to a FPV/RTV BID regimen. The FPV/RTV BID regimens used were based on preliminary plasma APV PK data available for the FPV/RTV QD regimens in these pediatric subjects. Since the plasma APV exposures achieved in 6 to 18 year old subjects receiving the FPV/RTV 30/6mg/kg QD regimen were similar to historical adult data for FPV/RTV 1400/200mg QD, a FPV/RTV 15/3 mg/kg BID regimen was used for subjects 6 to 18 years of age. Because plasma APV exposures achieved in 2 to 5 year old subjects receiving the FPV/RTV 30/6mg/kg QD regimen appeared to be approximately 25 % lower compared to historical adult data for FPV/RTV 1400/200 mg QD, a FPV/RTV 20/4 mg/kg BID regimen was implemented for subjects 2 to 5 years of age. Subjects receiving FPV/RTV 1400/200 mg QD were switched to the standard adult dosage regimen of FPV/RTV 700/100mg BID.

8. Dosage Regimen Adjustment Criteria

Dose Adjustment Due to Weight

Due to subjects' growth throughout the duration of the study, the dose of all drugs administered during the study were to be recalculated at each visit and the total daily dose adjusted according to the child's weight and the recommended dosage regimen. Dose adjustments were to occur when the dose would change by $\geq$ 10 % from the subject's prior calculated dose.

FPV/RTV QD Dose Adjustments Based on Week 4 PK Assessments

Individualized FPV dosage regimen adjustments, other than adjustments made for changes in weight or age, were made for subjects receiving the FPV oral suspension, based on their Week 4 plasma APV PK data. These individual FPV dosage regimen adjustments were made to ensure that target plasma APV concentrations were achieved.

The target plasma APV exposure for subjects receiving a FPV/RTV QD regimen was defined as a plasma APV C_τ of $\geq$ 1.02 µg/mL. This target represented the 25th percentile observed in adult subjects receiving AGENERASE 1200 mg QD + RTV 200 mg QD (study APV20001). Based on the Week 4 plasma APV PK data from at least 6 subjects who receive the FPV oral suspension, the dose of the FPV oral suspension was to be adjusted for all subjects in the cohort. If dose adjustment was necessary for the FPV oral

suspension, all subsequently enrolled subjects in the cohort would receive the newly recommended dose.

Potential Dose Adjustments for Switch Subjects Enrolled in Cohort 1 Receiving FPV/RTV BID and Reaching 6 years of age

During the study treatment period, "switch subjects" (subjects who switched from a QD regimen to a BID regimen), who were enrolled in Cohort 1 may have reached their sixth birthday. Accordingly, those subjects receiving the FPV 20 mg/kg and 4 mg/kg RTV BID regimen would undergo a dose adjustment to 15 mg/kg FPV BID in combination with 3 mg/kg RTV BID at the next scheduled study visit following their sixth birthday. If necessary, such a dose adjustment was delayed until after the subject completed their Week 4 PK assessments.

9. Sample Collection, Bioanalysis, and PK Assessments

Sample Collection

Subjects enrolled in Cohorts 1, 2, and 3 underwent serial plasma PK sampling on Week 4 over 24 hours (at 0, 1, 2, 4, 8, 12 and 24 hours post dosing). All subjects enrolled in the study had one plasma PK sample collected immediately prior to dosing (trough sampling) on Weeks 4, 8, 12, 24 and 48.

Subjects who switched from FPV/RTV QD to the FPV/RTV BID regimen had plasma PK samples collected immediately prior to dosing and 12 hours after dosing at the Week 4 post switch (PS) visit. Additionally, one plasma PK sample was collected immediately prior to dosing (trough sampling) on Weeks 8 PS, 12 PS, 24 PS and 48 PS and every 12 weeks thereafter.

Subjects or caregiver recorded the dates and times of the three FPV and RTV doses administered prior to collection of each pre-dose PK sample on the CRF.

Bioanalysis

Plasma samples were analyzed for APV and FPV by ⌜ ⌟ under the direction of Worldwide Bioanalysis, DMPK, GlaxoSmithKline, using a validated analytical method based on ⌜ ⌟ followed by HPLC/MS/MS analysis. The calibration range for plasma amprenavir was ⌜ ⌟ and the quality control (QC) concentrations used were 35, 1000, and 8500 ng/mL. Using 200 µL of human plasma, subsequently reduced to 50 µL, the lower limit of quantification (LLQ) for APV was 10 ng/mL and for FPV was 5 ng/mL and the higher limit of quantification (HLQ) for APV was 10,000 ng/mL and for FPV was 1000 ng/mL. The intra/inter day precision (% CV) for plasma amprenavir was ⌜ ⌟ %. The overall accuracy (% bias) for plasma amprenavir ranged from ⌜ ⌟

b(4)

Reviewer's Note:
The assay methodology is acceptable. The applicant acknowledges that since the trial is ongoing, some of the assay related information (e.g. intra/inter day precision, overall accuracy) may change upon completion of the studies.

PK Assessments

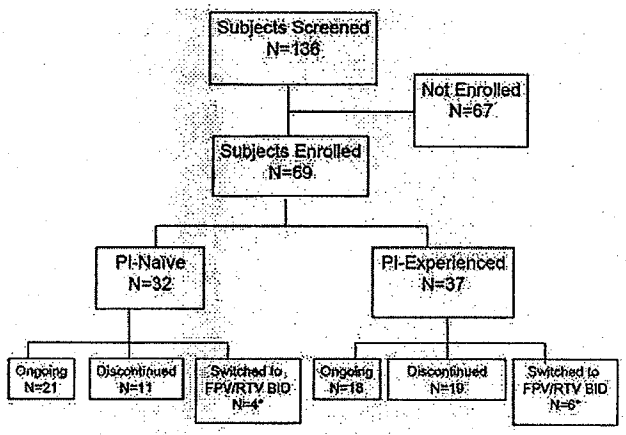
The standard deviation (SD) of log-transformed parameters, geometric mean and associated 95 % CI were included in the summary of plasma APV PK parameters. The plasma APV $AUC_{0-\tau}$, C_{max}, and C_{τ} were the primary pharmacokinetic endpoints.

10. Results

10.1 Subject Disposition

Fig 1 shows the subject disposition in the study.

Fig 1: Subject Disposition in the Study



*: switched subjects are also included in the ongoing and the discontinued populations

A total of 69 subjects were enrolled and received FPV/RTV QD. 10 subjects (6 subjects in the 2-5 year old group, 3 subjects in the 6-11 year old group, and 1 subject in the 12-18 year old group) switched to receive FPV/RTV BID during the study. Thirty (43 %) subjects discontinued FPV/RTV QD prematurely, of these, 10 (14 %) subjects withdrew due to adverse events.

Of the 69 subjects enrolled, 24 subjects (35 %) received the FPV tablet formulation and 45 subjects (65 %) received the FPV oral suspension. Of the subjects on tablets, 50 % (n = 12) discontinued at the time of analysis compared to 40 % (n = 18) of subjects receiving the FPV oral suspension who discontinued prematurely. Therefore, at the time of the analysis, there were 12 subjects on the tablet formulation and 27 subjects on the

suspension formulation. The reasons for premature discontinuation on the FPV tablets were insufficient viral load response (n = 4), subject decided to withdraw from the study (n = 2), AEs (n = 3) and withdrawal from the study due to other reasons. The premature discontinuations for subjects receiving the FPV oral suspension were due to an adverse event (n = 7), subject decided to withdraw (n = 2), protocol violation (n = 1), insufficient viral load response (n = 1) and other reasons (n = 7).

Table 3 shows the summary of demographic characteristics of the population (intent-to-treat).

Table 3: Summary of demographic characteristics of the population (intent-to treat population).

Age Groups	2-5 Years N=17	6-11 Years N=17	12-18 Years N=35	Total N=69
Age (years) Median (Min, Max)	4.0 (2,5)	9.0 (6, 11)	14.0 (12, 17)	12.0 (2, 17)
Median Weight, kg (range)	17 (11, 26)	25 (17, 55)	51 (33, 91)	34 (11, 91)
Median Height, cm (range)	102 (80, 125)	123 (103, 159)	160 (138, 180)	142 (80, 180)
Race				
White/Caucasian	6 (35)	5 (29)	24 (69)	35 (51)
Black	9 (53)	8 (47)	7 (20)	24 (35)
East & Southeast Asian	0	1 (6)	0	1 (1)
American Hispanic	2 (12)	3 (18)	3 (9)	8 (12)
Other	0	0	1 (3)	1 (1)

Source Data: Tables 6.12 and 8.61

10.2 Pharmacokinetic Results

Sixty-four (64) of the 69 enrolled subjects underwent plasma PK sampling during the study; all 64 subjects underwent PK trough sampling at various time points throughout the study and 40 of these subjects also underwent serial PK profile sampling at Week 4.

Table 4 shows the number of subjects included in the PK population.

Table 4: Number of Subjects Included in the PK Population in Study APV20003

		FPV/RTV Dosage Regimen								
		30/6 mg/kg QD			1400/200 mg QD		15/3 mg/kg BID		20/4 mg/kg BID	
	Overall	2-5 years	6-11 years	12-18 years	6-11 years	12-18 years	6-11 years	12-18 years	2-5 years	6-11 years
Number of Subjects in PK Concentration Population	84	16[1]	17[2,4]	15[2,4]	1[3]	25[3]	4	2	3[4]	
Number of Subjects in PK Parameter Population	59	15	16	11	1	20	4	2	3	
Number of Subjects in PK Summary Population (Cr)	57	15	15	10	1	19	4[4]	2	3	1[4]
Number of PK Samples Collected	611	166	171	87	6	126	20	5	9	
Number of Subjects Who Underwent PK Profile Sampling	40	16	12	6		5	NA			
Number of Subjects in PK Summary Population (Profile)	26	10	10	3		3				

Data Source: Table 17.12 and Table 17.13

1. Subject No. 6336 was enrolled into the 2-5 year old age group, but reached 6th birthday before Week 4 PK sampling and, thus, was included in the 6-11 year old age group for the PK populations.
2. Subject No. 7030 was enrolled into the 6-11 year old age group, but reached 12th birthday before Week 4 PK sampling and, thus, was included in the 12-18 year old age group for the PK populations.
3. Subject No. 7265 was enrolled into the 6-11 year old age group, but reached 12th birthday before providing evaluable PK data and, thus, was included in the 12-18 year old age group for the PK populations.
4. Some subjects provided data for more than one age group as they aged during the study.

40 subjects underwent serial PK profile sampling at Week 4. Of these 40 subjects, 26 subjects provided steady-state plasma APV PK parameters at a scheduled FPV/RTV QD dosage regimen. Of the 14 other subjects who underwent serial PK profile sampling, 7 subjects, whose week 4 pre-dose concentrations were below the lower quantification limit (BQL), were considered as having received only a single dose of FPV/RTV. Therefore, single dose plasma APV PK parameters were calculated for these subjects. The plasma APV PK parameters were not calculated for another 7 subjects because either the pre-dose concentration or 24-hour concentrations were extremely (at least 7-fold) different (N = 6 subjects) indicating that steady state had not been achieved, or because the samples were collected on the wrong day and time (N = 1 subject).

Fig 2 shows the mean plasma amprenavir concentration time profile for the 12-18 years old.

Fig 2: Mean Plasma APV Concentration-Time Profile in 12-18 years old

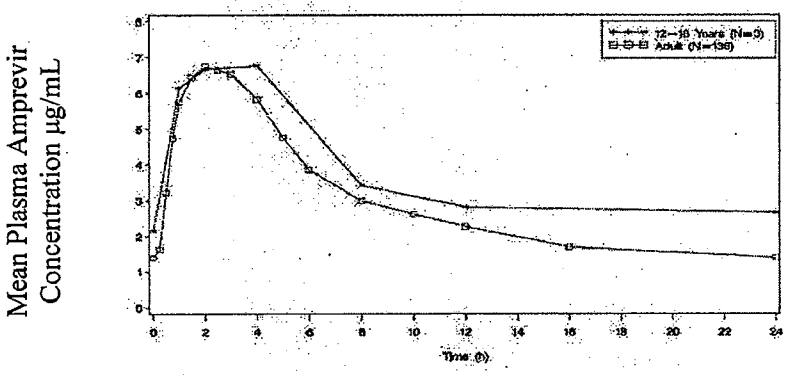


Fig 3: Mean Plasma APV Concentration-Time Profile (FPV 30 mg/kg QD + RTV 6 mg/kg QD)

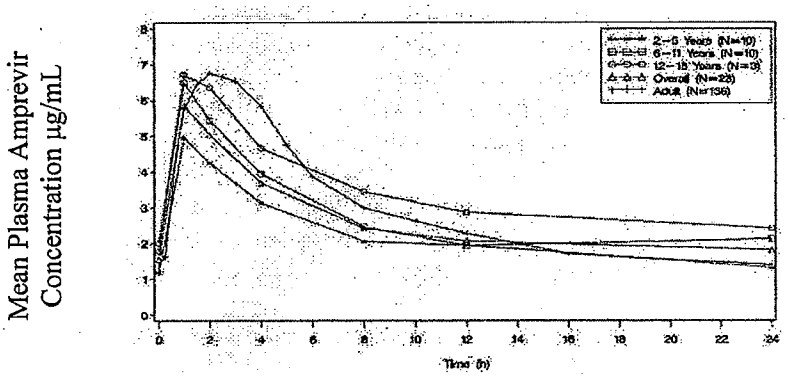


Table 5 shows the summary of steady state plasma APV pharmacokinetic parameters for FPV/RTV QD in subjects 2 to 18 years old in APV20003 and historical adult population.

Table 5: Summary of steady state plasma APV pharmacokinetic parameters for FPV/RTV QD in subjects 2 to 18 years old in APV20003 and historical adult population.

Plasma APV PK Parameter	FPV/RTV 30/6mg/kg QD (suspension)			FPV/RTV 1400/200mg QD (tablet)			
	2-5 Years N=15	6-11 Years N=15	12-18 Years N=10	6-11 Years N=1	12-18 Years N=19	Historical Adult Data[2]	
C_τ (µg/mL)	0.818 [0.577, 1.16] (124)	1.24 [0.832, 1.84] (201)	1.13 [0.749, 1.70] (138%)	2.15 [NA] (NA)	1.05 [0.744, 1.47] (181)	Healthy	1.29 [1.22, 1.37] (43)
						HIV	1.36 [1.21, 1.52] (61)

Plasma APV PK Parameter	FPV/RTV 30/6mg/kg QD (suspension)			FPV/RTV 1400/200mg QD (tablet)		
	2-5 Years N=10	6-11 Years N=10	12-18 Years N=3	12-18 Years N=3	Historical Adult Data[2]	
AUC(0-τ) (h*µg/mL)	47.3 [34.2, 65.4] (48)	49.5 [29.8, 82.1] (61)	75.5 [23.4, 244] (50)	71.8 [10.6, 486] (90)	Healthy	67.1 [64.7, 69.6] (27)
Cmax (µg/mL)	4.97 [3.76, 6.58] (41)	5.25 [2.81, 9.81] (107)	6.88 [4.31, 11.0] (19)	7.70 [2.70, 21.9] (44)	Healthy	7.42 [7.17, 7.68] (26)
tmax (h)	1.04 (0.95, 4.02)	1.07 (0.75, 2.07)	1.08 (0.92, 2.00)	3.78 (1.00, 4.00)	Healthy	2.00 (0.75, 5.00)
CL/F (mL/min/kg)	10.5 [7.62, 14.5] (47)	10.2 [6.21, 16.7] (78)	6.57 [2.08, 20.7] (49)	4.95 [0.745, 32.9] (89)	Healthy	4.16 [4.01, 4.32] (28)
CL/F (mL/min)	ND	ND	ND	278 [41.2, 1882] (50)	Healthy	298 [287, 309] (27)

Data Source: m5, study report RM2004/00512/01 Table 17.7 and Table 17.10

1. Geometric Mean [95% CI (CV%)], except tmax is presented as median (range)
2. Historical Adult Population: N=204 healthy adult subjects from Studies APV10009, APV10029, COL10053 for C_τ, AUC(0-τ), Cmax, tmax, and CL/F; N=97 HIV infected subjects from Studies APV30002 and APV30003 for C_τ.

ND = not determined

Table 6 shows the statistical summary of the plasma amprenavir pharmacokinetic parameters in APV20003.

Table 6: Statistical summary of the plasma amprenavir pharmacokinetic parameters in APV20003 [Ration of GLS means (90 % CI) Presented]

Plasma APV PK Parameter	FPV/RTV 30/6mg/kg QD			FPV/RTV 1400/200mg QD
	2-5 Years[1] vs Historical Adult[2]	6-11 Years[1] vs Historical Adult[2]	12-18 Years[1] vs Historical Adult[2]	12-18 Years[1] vs Historical Adult[2]
AUC(0-τ) (µg.h/mL)	0.695 (0.578-0.835)	0.727 (0.605-0.874)	1.11 (0.800-1.54)	1.06 (0.761-1.47)
Cmax (µg/mL)	0.663 (0.555-0.791)	0.699 (0.585-0.835)	0.917 (0.668-1.26)	1.03 (0.747-1.41)
C_τ (µg/mL)	0.700 (0.544-0.901)	0.903 (0.718-1.14)	0.844 (0.621-1.15)	0.755 (0.600-0.949)

Source Data: Table 17.11

1. Sample size for AUC(0-τ) and Cmax: N=10 for 2-5 years, N=10 for 6-11 years, N=3 for each 12-18 years old group; sample size for C_τ: N=15 for 2-5 years, N=15 for 6-11 years, N=10 for 12-18 years receiving FPV/RTV 30/6mg/kg QD, N=19 for 12-18 years receiving FPV/RTV 1400/200mg QD.
2. Sample size for Historical Adult Population: N=204 healthy adult subjects.

11. Safety

Please refer to the Medical Officer's Review.

12. Conclusion

- For 12 to 18 year old subjects receiving either the FPV/RTV 30/6mg/kg QD or the FPV/RTV 1400/200mg QD regimen, plasma APV $AUC_{0-\tau}$ and C_{max} was similar to adult subjects receiving FPV/RTV 1400/200mg QD. The C_τ estimates appeared approximately 20 % lower than values historically observed for adult subjects receiving FPV/RTV 1400/200mg QD.
- For 6 to 11 year old subjects receiving the FPV/RTV 30/6 mg/kg QD regimen, the mean plasma $APV_{0-\tau}$ AUC was 27 % lower and C_{max} was 30 % lower; whereas, C_τ appeared similar to values historically observed for adult subjects receiving FPV/RTV 1400/200 mg QD. Based on these PK results, 6-11 year old subjects would require a higher FPV/RTV QD dosage regimen. **However, the safety of the suspension formulation at higher doses (which *may* result in exposures similar to adult exposures) is currently unknown.**
- For 2 to 5 year old subjects receiving the FPV/RTV 30/6 mg/kg QD regimen, on average, plasma APV $AUC_{0-\tau}$ was 30 % lower, C_{max} was 34 % lower, and C_τ was 30 % lower than values historically observed for adult subjects receiving FPV/RTV 1400/200 mg QD. Based on these PK results, 2-5 year old subjects would require a higher FPV/RTV QD dosage regimen. **However, the safety of the suspension formulation at higher doses (which *may* result in exposures similar to adult exposures) is currently unknown.**

APV29005

1. Title

A 48 Week, Phase II, Non-Comparative, Open-Label, Multi-Cohort, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of GW433908 (Fosamprenavir)/Ritonavir BID when Administered to HIV-1 Infected, PI-Naïve and Experienced, Pediatric Subjects, 2 to 18 Years Old and of FPV BID Administered to PI-Naïve, Pediatric Subjects 2 to < 6 Years Old.

2. Objectives

The clinical pharmacology related objectives of this trial were:

- To define the FPV/RTV BID dosing regimen which will provide target steady-state plasma amprenavir (APV) exposure to pediatric subjects 2 to 18 years of age
- To define the FPV BID dosing regimen which will provide target steady-state plasma APV exposure to pediatric subjects 2 to 5 years of age
- To assess plasma FPV exposure when administered to HIV-1 infected pediatric subjects 2 to 18 years of age.

3. Study Design

Table 1 shows the study design.

Table 1: Summary of Study Design for APV29005

Cohort	Age[1]	Treatment Status	Regimen[2]	Number of Subjects[5]
1A[3]	2 to 5 years	PI-naïve	FPV BID	7 + ≥12
1B[3]	2 to 5 years	PI-naïve or experienced	FPV/RTV BID	16
2[3]	6 to 11 years	PI-naïve or experienced	FPV/RTV BID	8 + ≥8
3[3]	12 to 18 years	PI-naïve or experienced	FPV/RTV BID	10
4[4]	2 to 18 years	PI-naïve or experienced	FPV/RTV BID	Up to 24

1. Subjects enrolled up to one month before 6th birthday (Cohorts 1A and 1B), one month before 12th birthday (Cohort 2), and one month before 19th birthday (Cohorts 3 and 4). Enrolment = Baseline/Day 1.
2. GlaxoSmithKline (GSK) provided optional ABC and/or 3TC to all subjects for use in constructing an active nucleoside reverse transcriptase inhibitor (NRTI) background regimen.
3. Cohorts 1A, 1B, 2 and 3 enrolled in parallel. Subjects in these cohorts had a PK profile on Week 2 and PK trough sampling on Weeks 4, 8, 12, 16, 24, 36 and 48 and every 12 weeks thereafter.
4. Subjects in Cohort 4 had PK trough sampling on Weeks 2, 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter.
5. Where two numbers were provided, the first represents the initial number of subjects who provided PK data at Week 2 which contributed to determination of the revised dose for the cohort. The second number represented the number of subjects required on the revised dose regimen.

Table 2 shows the number of subjects included in the analysis.

Table 2: Number of Subjects Included in the Analysis.

	Overall	FPV BID Dosage Regimen			FPV/RTV BID Dosage Regimen							
		30mg/kg		40mg/kg	20/4mg/kg		15/3mg/kg		18/3mg/kg		700/100mg	
		2-5 years	6-11 years	2-5 years	2-5 years	6-11[1] years	6-11 years	12-18 years	6-11 years	12-18 years	6-11 years	12-18 years
Number of Subjects in PK Concentration Population	70	17	1	10	1	2	12	7	18	2	4	28
Number of Subjects in PK Summary Population (Cτ)	67	17	1	10	1	1	12	7	17	2	4	24
Number of Subjects in PK Summary Population (Profile)	51	8	0	7	1	1	10	4	9	0	3	8
Number of PK Samples Collected	798	135	1	95	10	17	97	48	128	7	39	221

Subjects in Cohort 1A (2 to 5 years) initiated dosing with FPV BID (40 mg/kg) and subjects in Cohorts 1B (20/4 mg/kg BID), 2 (15/3 mg/kg BID), and 3 (15/3 mg/kg or 700/100 mg BID) initiated dosing with FPV/RTV BID. The first 6 to 10 subjects in each cohort initiated a dosage regimen based on previous APV and FPV pediatric studies; whereas, subsequently enrolled subjects initiated a dosage regimen based on PK data from the first 6 to 10 subjects enrolled in the cohort. For all subjects, the dosage regimen may have been adjusted based on the individual's steady-state PK results collected at Week 2 or later.

Reviewer's Note:

The protocol of this study was amended on two occasions. The text below highlights the clinical pharmacology related amendments.

Amendment # 1 (Sep 13, 2004)-1 subject was enrolled in the study at the time of the amendment.

- *Revision to the protocol to allow investigators to receive expedited Week 2 PK results on all subjects in Cohorts 1A, 1B, 2 and 3 and not just on approximately the first six subjects from each cohort as previously stated.*
- *Clarification on the maximum daily dosing of FPV tablets/oral suspension and RTV capsules/oral solution. For subjects who weighed at least 47 kg, the maximum allowed daily dose of FPV tablets was 1400 mg BID or 700 mg/100 mg RTV b.i.d. For subjects who weighed at least 33 kg the maximum daily dose of RTV capsules was 200 mg (100 mg BID). For those who did not meet the specified weight criteria, the maximum daily dosing of FPV oral suspension was 2800 mg or 1800 mg with RTV and for RTV oral solution was 200 mg. These maximum daily doses for FPV and RTV formulations were excluded from the original protocol.*

The applicant states that the goal of amendment # 1 was to allow the investigators an opportunity to review PK results for all subjects and to reiterate the maximum daily doses of the FPV and RTV formulation that could be administered safely to subjects.

Amendment # 2 (Jan 18, 2006)-73 subjects were enrolled in the study at the time of the amendment.

- *Following the PK analysis of the first eight to ten subjects in Cohorts 1A and 2, a revised dose for each of these cohorts was determined. These revised doses were to be administered to subjects already enrolled in these specific cohorts and to any subsequently enrolled subjects. For e.g.,* ***Cohort 1A (2 to 5 years, FPV BID)*** *subjects initiated dosing with FPV 40 mg/kg BID. The steady-state PK data from the first 7/8 subjects indicated a cohort dose revision to FPV 30 mg/kg BID regimen, and newly enrolled subjects initiated chronic dosing with the 30 mg/kg regimen. Similarly,* ***Cohort 2 (6 to 11 years, FPV/RTV BID)*** *subjects initiated dosing with FPV/RTV 15/3mg/kg BID. Steady-state PK data from the first eight subjects indicated a cohort dose revision to FPV/RTV 18/3mg/kg BID regimen, and newly enrolled subjects initiated chronic dosing with this regimen.*

- *Lowering of the weight criterion for subjects taking FPV tablets. Previously, in Cohort 2, the FPV dose was 15 mg/kg (+RTV) which meant subjects had to weigh at least 47kg to receive the FPV 700mg tablets. However, since the new revised FPV dose had increased to 18 mg/kg (+RTV); subjects only had to weigh at least 39 kg to be able to switch to the FPV tablet formulation.*

- *Clarification that switching of subjects from FPV BID to FPV/RTV BID in Cohort 1A after the Week 2 visit was only allowed in countries where RTV oral solution is approved and locally prescribed.*

4. Selection of Study Population

HIV-1 infected, PI-naïve and PI-experienced subjects aged 2 to 18 years with screening viral HIV-1 RNA ≥ 400copies/mL and who met the eligibility criteria were recruited into the study. All PI-naïve subjects, including ART-naïve subjects, were eligible for this study. PI-experienced subjects were eligible if they had previously been treated with three PIs or less, excluding Agenerase (amprenavir) and FPV. Prior therapy with a RTV-boosted PI regimen was considered as only one prior PI as long as the RTV dose was below that recommended for use as an antiretroviral agent. Subjects were not permitted to receive concurrent tenofovir disoproxil fumarate (TDF), non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy or PI therapy other than FPV/RTV or FPV while participating in this study

5. Drugs Used in the Trial

Table 2 shows the batch number of the tablet and suspension formulations used in the study.

Table 2: Batch number of the tablet and suspension formulations used in the study.

Drug Name	Manufacturer	Batch Numbers
FPV (700mg) tablets[1]	GSK, Ware, Hertfordshire, UK	B075829, B110562, B117130, B121918, B130777, R196231
FPV (50mg/mL) oral suspension[1]	GSK, Mississauga, Ontario, Canada	3K040, 3K041, 4B001, 4E002, 5A002, 5C005

1. Includes all batch numbers for the FPV formulations used by the time of report writing for all subjects in APV29005.

6. Dosage and Administration

FPV oral suspension and RTV oral solution were administered *via* separate dosing syringes. The administration of the FPV suspension and RTV oral solution *via* dosing cups was not allowed as residual FPV oral suspension and RTV oral solution could remain in the cups. The FPV suspension was to be shaken as per the label instructions prior to measuring. The shaking instructions were as follows; shake vigorously for 20 seconds before the first dose is removed from the bottle, and 5 seconds before each subsequent dose. The results from study APV10016 showed that administration of the suspension formulation and tablet formulation under fasted conditions provided similar exposures. The administration of the suspension formulation provided lower exposures as compared to administration of the suspension formulation under fasting conditions. However, **the FPV oral suspension and RTV oral solution were recommended to be administered with food to accommodate the frequent eating schedule of children, to enhance the adherence through taste masking with food, and to improve tolerability. Therefore, higher doses of the suspension formulation (higher than the doses that would be predicted based on the adult doses and the molar equivalency between fosamprenavir and amprenavir) were administered to the pediatric subjects to "compensate" for the reduction in systemic exposures after administration of the suspension formulation with food.**

Fosamprenavir oral tablet and RTV oral capsule formulations could be administered without regard to food but it was detailed that administration with food may improve tolerability. FPV oral tablets and RTV oral capsules were to be administered whole (i.e. FPV tablets could not be broken and RTV capsules could not be opened). Subjects only received one formulation of FPV at any given time (i.e. one could not receive FPV tablets and FPV oral suspension simultaneously to achieve adequate FPV dosing). Similarly, subjects only received one formulation of RTV at any given time.

The dosing of study drugs on the evening prior to the Week 2 visit was observed and the Week 2 visit doses were administered at the site. All other doses were administered on an out-patient basis.

Cohort 1A (2 to 5 years, FPV BID) subjects initiated dosing with FPV 40mg/kg BID. Steady-state PK data from the first 7/8 subjects indicated a cohort dose revision to FPV

30 mg/kg BID regimen, and newly enrolled subjects initiated chronic dosing with the 30 mg/kg regimen.

Cohort 1B (2 to 5 years, FPV/RTV BID) subjects initiated dosing with FPV/RTV 20/4mg/kg BID. Only three subjects had been recruited as of the cut-off date therefore subjects are continuing to be enrolled into this cohort.

Cohort 2 (6 to 11 years, FPV/RTV BID) subjects initiated dosing with FPV/RTV 15/3mg/kg BID. *Steady-state PK data from the first eight subjects indicated a cohort dose revision to FPV/RTV 18/3mg/kg BID regimen, and newly enrolled subjects initiated chronic dosing with this regimen.*

For Cohort 3 (12 to 18 years, FPV/RTV BID), the majority of subjects in this age group are receiving the standard adult regimen of FPV/RTV 700/100 mg BID regimen whereas, a few received the FPV oral suspension at a dose of FPV/RTV 15/3 mg/kg BID. No dose change was implemented.

7. Plasma APV PK Targets

Steady-state plasma APV PK parameters obtained from adult subjects who received FPV 1400mg BID or FPV/RTV 700/100mg BID in the following studies were combined to serve as Historical Control Adult PK Population: for FPV 1400mg BID: APV20001, APV10013, APV10023, APV10024, and APV10031; for FPV/RTV 700/100mg BID: APV10010, APV10011, APV10012, APV10013, APV10018, APV10022, APV10026, APV10028, APV10031, and APV30003 (C_τ only): for RTV PK Studies APV10010, APV10018, and APV10028 were included in the historical control group.

For subjects receiving repeat doses of FPV BID, target PK was defined as a plasma APV C_τ value of $\geq$ 0.25µg/mL, representing the 25th percentile observed in adult subjects receiving FPV 1395mg BID in APV20001 (previous clinical study conducted with amprenavir).

For subjects receiving repeat doses of FPV/RTV BID, target PK was defined as a plasma APV C_τ value of $\geq$ 1.48µg/mL, representing the 25th percentile observed in adult subjects receiving FPV/RTV 700/100mg BID in Studies APV10010, APV10011, APV10012, APV10013, and APV10022.

To ensure that the pediatric subjects did not maintain concentrations (C_{max} and C_τ) and exposures ($AUC_{0-\tau}$) higher than those observed in adults, an upper PK target was defined as a plasma APV $AUC_{0-\tau}$ of 61.68 µg.h/mL at the Week 2 visit or a plasma APV C_τ value of 3.52 µg/mL at subsequent visits (where only trough sampling was conducted), representing the 95th percentile observed in adults receiving FPV/RTV 700/100mg BID.

8. Dose Rationale

The selection of the initial FPV and FPV/RTV BID dosage regimens was based on preliminary plasma APV PK data from another FPV pediatric study APV20003 where a regimen of FPV/RTV 30/6mg/kg QD was evaluated.

- Plasma APV exposures achieved in 6 to 18 year old subjects who received FPV/RTV 30/6 mg/kg QD appeared to be similar to historical adult data for FPV/RTV 1400/200 mg QD; therefore, a FPV/RTV 15/3 mg/kg BID regimen was used for subjects 6 to 18 years of age (Cohorts 2 and 3).

- Plasma APV exposures achieved in 2 to 5 year old subjects receiving the FPV/RTV 30/6 mg/kg QD regimen appeared to be approximately 25 % lower compared to historical adult data for FPV/RTV 1400/200 mg QD; therefore a FPV 20/4 mg/kg BID regimen was used for subjects 2 to 5 years of age (Cohort 1B).

- Based on the initial FPV/RTV 20/4 mg/kg BID regimen selected for subjects in Cohort 1B (2 to 5 years) and the higher FPV doses used without RTV in adults, the initial FPV BID dosage regimen administered to subjects 2 to 5 years old (i.e. Cohort 1A) was FPV 40 mg/kg BID.

The FPV BID regimen was not evaluated in the older children (i.e. 6 to 18 years old) because the amprenavir data is available from previous studies and investigators would not enroll older patients on un-boosted fosamprenavir.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Subjects in Cohorts 1A, 1B, 2, and 3 underwent steady-state PK sampling over 12 hours at the Week 2 visit (at 0 hours [pre-dose] and at 1, 2, 4, 6, 8 and 12 hours post-dose). Subjects in Cohort 4 underwent PK trough sampling at Week 2. All subjects (Cohorts 1A, 1B, 2, 3, and 4) underwent PK trough sampling at Weeks 4, 8, 12, 16, 24, 36, 48 and every 12 weeks thereafter. Plasma PK samples were analyzed for APV, FPV, and RTV (where applicable).

Bioanalysis

Plasma samples were analyzed for APV by Worldwide Bioanalysis-Research Triangle Park (RTP), NC using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography with ⌜ ⌟ b(4)
(HPLC/MS/MS) analysis. The calibration range for plasma amprenavir was ⌜
⌟ and the quality control concentrations for amprenavir was ⌜ ⌟
ng/mL. The lower limit of quantification (LLQ) and higher limit of quantification (HLQ)

for FPV were 5 ng/mL and 100 ng/mL and for APV and RTV were 10 ng/mL and 10, 000 ng/mL. The intra/inter day precision (% CV) for amprenavir was [ ]
The overall accuracy (% bias) for amprenavir ranged from [ ]

b(4)

Reviewer's Note:

The assay methodology is acceptable. The applicant acknowledges that since the trial is ongoing, some of the assay related information (e.g. intra/inter day precision, overall accuracy) may change upon completion of the studies.

Pharmacokinetic Assessments

Plasma APV and RTV PK parameters, except t_{max}, were log-transformed prior to statistical analysis of the PK data. Steady-state plasma APV and RTV pre-dose concentrations were considered a C_τ value if the PK sample was collected between 8 to 16 hours since the last dose for a BID regimen. *Since very few FPV concentrations were quantifiable, plasma FPV PK parameters were not estimated.*

Statistical Analysis

Statistical comparisons were conducted for PK data between each pediatric age group (i.e. 2 to 5 years, 6 to 11 years, and 12 to 18 years) and the historical adult population. In addition, statistical comparisons were made between dosage regimens within each age group.

Analysis of variance (ANOVA), considering the combination of age group and dosage regimen as a fixed effect, was performed on log-transformed plasma $AUC_{0-\tau}$, CL/F, C_{max}, and C_τ to compare plasma APV and RTV PK parameters between each pediatric age group/dosage regimen to historical adult data. Results from these analyses were exponentiated to obtain a point estimate and 90 % CI estimate of the test (pediatric)-to-reference (historical adult) ratio of GLS means.

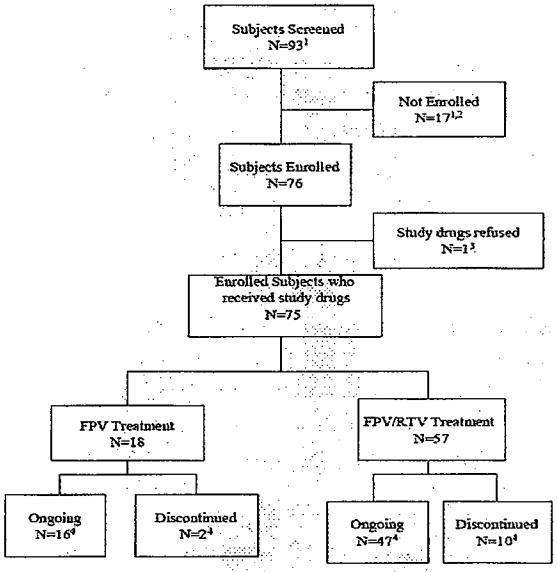
ANOVA, considering dosage regimen as a fixed effect, was performed on log-transformed plasma APV $AUC_{0-\tau}$, C_{max}, and C_τ to compare plasma APV PK parameters between dosage regimens within an age group, including FPV 40 mg/kg BID vs. FPV 30 mg/kg BID in the 2 to 5 year age group and FPV/RTV 18/3mg/kg BID vs. FPV/RTV 15/3mg/kg BID in the 6 to 11 year age group.

10. Results

10.1 Subject Disposition

Fig 1 shows the subject disposition in the study.

Fig 1: Subject Disposition in APV29005



Source Data: Table 6.2 and Table 6.8.

1. Two subjects (Subjects 330 and 60) were screened twice; therefore 93 unique subjects were actually screened.
2. Reasons for not enrolling included did not fulfill the eligibility criteria n=8, genotype/phenotype not suitable for study n=9, weight <33kg, n=1, and subject could not comply with study requirements as taking psychotic medications and the dose would have to be halved to be on-study, n=1.
3. Subject 281 refused to take the first dose of study drugs and withdrew from the study. Study drugs are FPV and RTV.
4. As of the cut-off date 22 May 2006 for this report.

Table 3 shows the summary of the treatment discontinuation by age group at entry.

Table 3: Summary of Treatment Discontinuation by Age Group at Entry for APV29005

Age at Entry	2-5 years N=21	6-11 years N=25	12-18 years N=29	Total N=75
No. Subjects Enrolled and Treated	21	25	29	75
No. (%) Subjects Prematurely Discontinuing	3 (14)	5 (20)	4 (14)	12 (16)
No. (%) Ongoing	18 (86)	20 (80)	25 (86)	63 (84)
Primary Reason for Premature Discontinuation of PI, n (%):				
AE	1 (5)	0	1 (3)	2 (3)
Subject decided to withdraw	0	2 (8)	0	2 (3)
Insufficient viral load response	1 (5)	0	0	1 (1)
Other	1 (5)	3 (12)	3 (10)	7 (9)

Of the 75 enrolled subjects who received study medication, 27 subjects received FPV tablets (all in the FPV/RTV group) and 48 subjects received FPV oral suspension (18 subjects in the FPV group and 30 in the FPV/RTV group) at study entry. However, during the study, 8 subjects switched from FPV oral suspension to FPV tablets, such that, as of the cut-off date for the report, 35 subjects (47 %) were receiving FPV tablets or had discontinued while receiving tablets and 40 subjects (53 %) were receiving FPV oral suspension or had discontinued while receiving oral suspension. Of the subjects who received FPV tablets, 14 % (5/35) had discontinued by the time of data cut-off compared with 18 % (7/40) of subjects receiving the FPV oral suspension discontinued prematurely in the same period.

Table 4 shows the number of subjects included in each of the plasma APV PK population.

Table 4: Number of Subjects Included in the APV PK Populations in APV29005

		FPV BID Dosage Regimen			FPV/RTV BID Dosage Regimen							
		30mg/kg		40mg/kg	20/4mg/kg		15/3mg/kg		18/3mg/kg		700/100mg	
	Overall	2-5 years	6-11 years	2-5 years	2-5 years	6-11[1] years	6-11 years	12-18 years	6-11 years	12-18 years	6-11 years	12-18 years
Number of Subjects in PK Concentration Population	70	17	1	10	1	2	12	7	18	2	4	28
Number of Subjects in PK Summary Population (Cr)	67	17	1	10	1	1	12	7	17	2	4	24
Number of Subjects in PK Summary Population (Profile)	51	8	0	7	1	1	10	4	9	0	3	8
Number of PK Samples Collected	798	135	1	95	10	17	97	48	128	7	99	221

Source Data: Table 10.1
Some subjects provided data for more than one age group as they aged through the study.
1. Subject 79 was enrolled into the 2-5 year old age group to receive FPV/RTV 20/4mg/kg BID, but reached 6th birthday before Week 2 PK sampling

Reviewer's Note:

Since only one subject in the 2-5 year age group provided data for the FPV/RTV BID, this subject's PK was not discussed in the report.

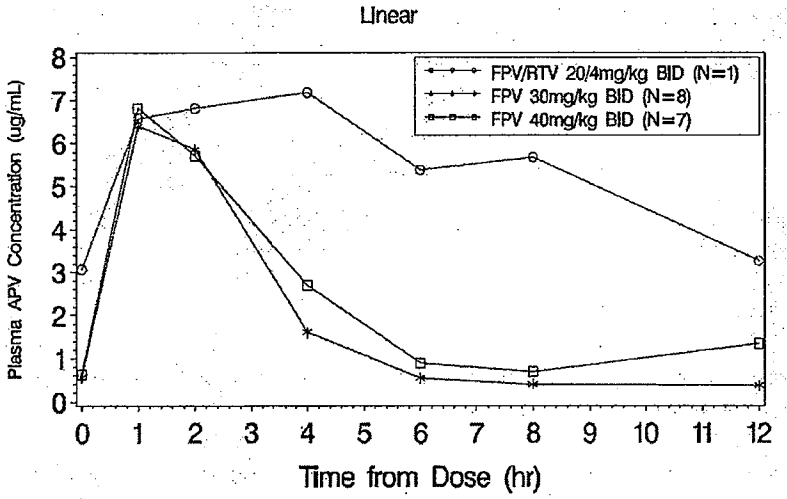
Table 5 shows the demographics for the PK summary population. The PK summary population is comprised of subjects who provided a full concentration-time profile.

Table 5 shows the demographics for the PK summary population.

	2-5yrs (n = 19)	6-11yrs (n = 24)	12-18yrs (n = 29)	Total (N = 67)
Gender (Male/Female)	4/15	12/12	15/14	29/38
Age (yrs) (mean ± sd)	3 ± 1.15	8.4 ± 2.02	13.7 ± 1.78	9 ± 4.76
Height (cm) (mean ± sd)	93.2 ±9.38	128.2 ± 12.39	157 ±10.76	130 ± 28.52
Weight (kg) (mean ± sd)	15 ± 4.36	30.9 ±9.13	53 ±13.6	35.4 ±19.10

Fig 2 (A, B, and C) shows the mean plasma amprenavir concentration-time profile by age group.

Fig 2A: Mean Plasma APV Concentration-Time Profile in 2-5 years old



Appears This Way
On Original

Fig 2B: Mean Plasma APV Concentration-Time Profile in 6-11 years old

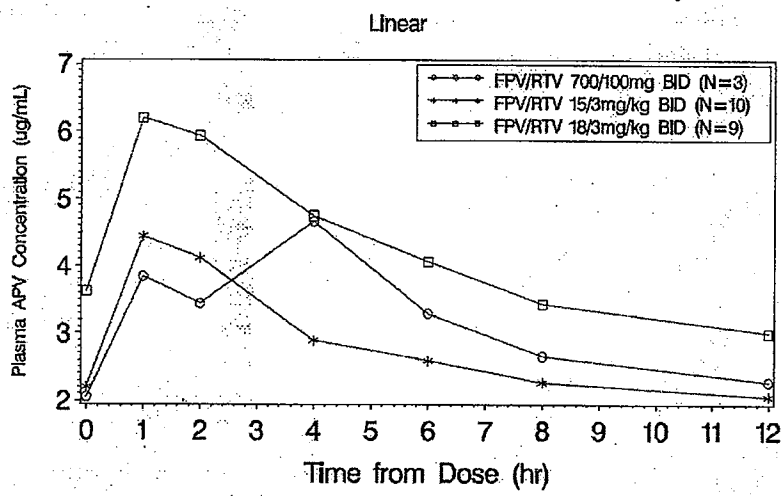
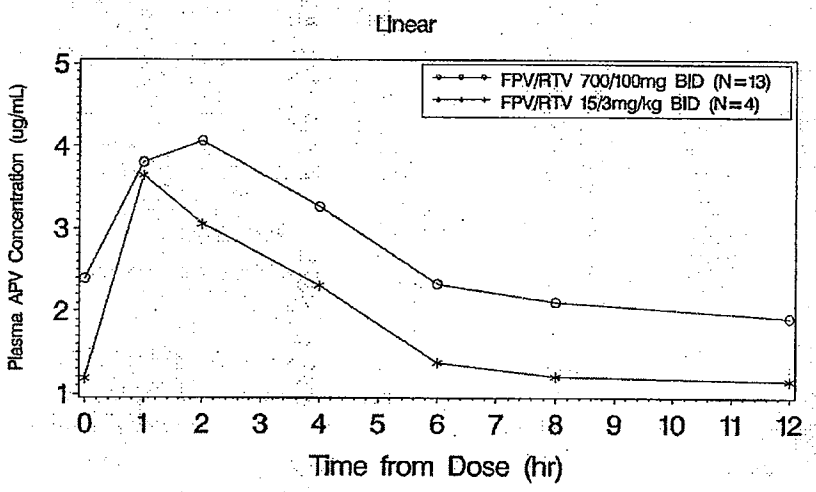


Fig 2C: Mean Plasma APV Concentration-Time Profile in 12-18 years old



11. Comparison between Pediatric Subjects and Historical Adult Data

FPV BID Regimens, Pediatric Subjects 2-5 years old

Table 6 shows the summary of the steady-state plasma APV pharmacokinetic parameters and statistical comparisons for the FPV BID in pediatric subjects 2-5 years old in APV29005 and historical adults.

Table 6: Summary of the steady-state plasma APV pharmacokinetic parameters and statistical comparisons for the FPV BID in pediatric subjects 2-5 years old in APV29005 and historical adults.

Plasma APV PK Parameter	2 to 5 Years[1]		Historical Adult 1400mg BID[1,3,4] N=189	2 to 5 Years vs. Historical Adult[2,4]	
	30mg/kg BID N=8[3]	40mg/kg BID N=7[3]		30mg/kg BID	40mg/kg BID
AUC(0-τ) (h.µg/mL)	15.7 (6.83, 36.2) [130]	24.1 (15.2, 38.0) [53]	17.6 (16.7, 18.5) [44]	0.893 (0.689, 1.16)	1.37 (1.04, 1.81)
Cmax (µg/mL)	5.00 (1.95, 12.8) [160]	6.52 (4.47, 9.51) [43]	5.06 (4.82, 5.32) [42]	0.988 (0.766, 1.27)	1.29 (0.983, 1.69)
Cτ (µg/mL)	0.454 (0.342, 0.604) [60]	0.710 (0.424, 1.19) [83]	0.291 (0.271, 0.312) [61]	1.28 (1.11, 1.48)	1.96 (1.57, 2.45)
CL/F (mL/min/kg)	27.5 (12.0, 63.0) [130]	23.4 (14.9, 36.8) [52]	15.7 (14.9, 16.4) [40]	1.76 (1.37, 2.24)	1.49 (1.15, 1.94)
CL/F (mL/min)	397 (163, 967) [145]	330 (203, 538) [57]	1137 (1079, 1197) [44]	0.349 (0.269, 0.454)	0.290 (0.220, 0.384)
tmax (h)	1.17 (1.00,3.92)	1.00 (0.75, 2.00)	1.50 (0.50, 5.00)	ND	ND
t1/2 (h)	3.05 (1.99,4.68) [54]	3.99 (2.13, 7.49) [54]	ND	ND	ND

Source Data: Table 10.9, Table 10.11, and Table 10.13
ND = not done
1. Geometric Mean (95% CI) [CVb%], except tmax is presented as median (range)
2. GLS Mean Ratio (90% CI)
3. N=17 for 30mg/kg BID Cτ, N=10 for 40mg/kg BID Cτ and N=5 for 40mg/kg BID t1/2, N=190 for historical adult Cτ
4. Healthy Adults

Compared to the historical adult population receiving FPV 1400mg BID, pediatric subjects, 2 to 5 years old, receiving FPV 30mg/kg BID had 11 % lower plasma APV $AUC_{0-\tau}$, similar C_{max}, and 28 % higher C_τ values; whereas, those receiving 40 mg/kg BID had 37 % higher $AUC_{0-\tau}$ values, 29 % higher C_{max} values and 96 % higher C_τ values.

Pediatric subjects, 2 to 5 years old receiving FPV 40mg/kg BID (33 % increase in dose over the 30 mg/kg dose) had 53 % higher plasma APV $AUC_{0-\tau}$, 31 % higher C_{max}, and 53 % higher C_τ values compared to subjects receiving FPV 30mg/kg BID.

FPV/RTV BID Regimens, Pediatric Subjects 6-11 years old

Table 7 shows the summary of the steady-state plasma APV pharmacokinetic parameters and statistical comparisons for the FPV/RTV BID in pediatric subjects 6 to 11 years old in APV29005 and historical adults.

Table 7: Summary of the steady-state plasma APV pharmacokinetic parameters and statistical comparisons for the FPV/RTV BID in pediatric subjects 6 to 11 years old in APV29005 and historical adults.

Plasma APV PK Parameter	6 to 11 Years[1]			Historical Adult	6 to 11 Years vs. Historical Adult[2,5]		
	15/3mg/kg BID N=10[3,4]	18/3mg/kg BID N=9[3,4]	700/100mg BID N=3[4]	700/100mg BID N=159[3,5]	15/3mg/kg BID	18/3mg/kg BID	700/100mg BID
AUC(0-τ) (h.µg/mL)	32.2 (23.0, 45.0) [46]	46.7 (33.9, 64.3) [44]	37.7 (22.1, 64.1) [22]	37.0 (35.1, 38.9) [33]	0.871 (0.718, 1.06)	1.26 (1.04, 1.53)	1.02 (0.734, 1.42)
Cmax (µg/mL)	4.34 (3.16, 5.96) [47]	6.07 (4.40, 8.38) [44]	5.85 (3.94, 8.70) [16]	5.62 (5.35, 5.92) [33]	0.772 (0.642, 0.928)	1.08 (0.890, 1.31)	1.04 (0.749, 1.45)
Cτ (µg/mL)	2.08 (1.47, 2.94) [59]	2.69 (2.15, 3.36) [45]	1.79 (0.340, 9.42) [140]	2.17 (2.05, 2.30) [38]	0.952 (0.743, 1.22)	1.03 (0.849, 1.25)	0.835 (0.605, 1.15)
CL/F (mL/min/kg)	6.50 (4.70, 8.99) [44]	5.42 (3.94, 7.46) [43]	5.92 (2.58, 13.6) [34]	3.52 (3.33, 3.71) [35]	1.85 (1.51, 2.26)	1.54 (1.26, 1.88)	1.68 (1.20, 2.37)
CL/F (mL/min)	195 (137, 279) [49]	160 (99.2, 259) [69]	265 (156, 452) [22]	270 (257, 284) [33]	0.723 (0.591, 0.885)	0.594 (0.485, 0.726)	0.983 (0.698, 1.38)
tmax (h)	2.00 (1.00, 6.00)	1.00 (0.50, 4.00)	3.92 (1.00, 4.02)	1.50 (0.50, 8.00)	ND	ND	ND
t1/2 (h)	10.8 (8.90, 13.1) [25]	10.1 (6.68, 15.2) [52]	9.54 (3.08, 29.6) [48]	ND	ND	ND	ND

Source Data: Table 10.9, Table 10.11, and Table 10.13
ND = not done
1. Geometric Mean (95% CI) [CV%], except tmax is presented as median (range)
2. GLS Mean Ratio (90% CI)
3. N=9 for 15/3mg/kg BID AUC(0-τ), CL/F and t1/2, N=8 for 18/3mg/kg BID t1/2, N=158 for historical adult AUC(0-τ) and N=157 for historical adult CL/F
4. N=12 for 15/3mg/kg BID Cτ, N=17 for 18/3mg/kg BID Cτ and N=4 for 700/100mg BID Cτ
5. Healthy Adults

Compared to the historical adult population receiving FPV/RTV 700/100mg BID, pediatric subjects, 6 to 11 years old, receiving FPV/RTV 15/3mg/kg BID had 13 % lower plasma APV $AUC_{0-\tau}$ and 23 % lower C_{max} values, but similar C_τ values; whereas, subjects receiving FPV/RTV 18/3 mg/kg BID had 26 % higher $AUC_{0-\tau}$ and similar C_{max} and C_τ values. Three 6 to 11 year old subjects who weighed at least 39 kg received the standard adult dosage regimen of FPV/RTV 700/100mg BID and had similar plasma APV $AUC_{0-\tau}$ and C_{max} values, but 16 % lower C_τ values compared to adult values.

Pediatric subjects, 6 to 11 years old receiving FPV/RTV 18/3 mg/kg BID (20 % increase in dose over the 15 mg/kg dose) had 45 % higher plasma APV $AUC_{0-\tau}$, 40 % higher C_{max}, and similar C_τ values compared to subjects receiving FPV/RTV 15/3mg/kg BID.

FPV/RTV BID Regimens, Pediatric Subjects 12-18 years old

Table 8 shows the summary of the steady-state plasma APV pharmacokinetic parameters and statistical comparisons for the FPV/RTV BID in pediatric subjects 12 to 18 years old in APV29005 and historical adults.

Table 8: Summary of the steady-state plasma APV pharmacokinetic parameters and statistical comparisons for the FPV/RTV BID in pediatric subjects 12 to 18 years old in APV29005 and historical adults.

Plasma APV PK Parameter	12 to 18 Years[1]		Historical Adult	12 to 18 Years vs. Historical Adult[2,5]	
	700/100mg BID N=8[4]	15/3mg/kg BID N=4[4]	700/100mg BID N=159[1,3,5]	700/100mg BID	15/3mg/kg BID
AUC(0, τ) (h.µg/mL)	29.4 (19.4, 44.5) [53]	21.8 (18.0, 26.3) [12]	37.0 (35.1, 38.9) [33]	0.795 (0.648, 0.974)	0.589 (0.443, 0.782)
Cmax (µg/mL)	4.33 (2.82, 6.65) [55]	3.92 (2.44, 6.29) [30]	5.62 (5.35, 5.92) [33]	0.770 (0.628, 0.945)	0.697 (0.524, 0.927)
Cτ (µg/mL)	1.61 (1.21, 2.15) [77]	1.29 (0.619, 2.71) [94]	2.17 (2.05, 2.30) [38]	0.803 (0.693, 0.931)	0.673 (0.509, 0.890)
CL/F (mL/min/kg)	6.06 (3.87, 9.48) [58]	10.0 (8.07, 12.5) [14]	3.52 (3.33, 3.71) [35]	1.72 (1.39, 2.13)	2.85 (2.12, 3.84)
CL/F (mL/min)	340 (225, 515) [53]	392 (356, 431) [6]	270 (257, 284) [33]	1.26 (1.02, 1.56)	1.45 (1.08, 1.95)
tmax (h)	2.00 (0.00, 4.00)	1.00 (1.00, 2.00)	1.50 (0.50, 6.00)	ND	ND
t1/2 (h)	9.11 (5.85, 14.2) [57]	9.72 (2.23, 42.4) [116]	ND	ND	ND

Source Data: Table 10.9, Table 10.11, and Table 10.13
ND = not done
1. Geometric Mean (95% CI) [CV%], except tmax is presented as median (range)
2. GLS Mean Ratio (90% CI)
3. N=158 for historical adult AUC(0-τ) and N=157 for historical adult CL/F
4. N=24 for 700/100mg BID Cτ, N=7 for 15/3mg/kg BID Cτ
5. Healthy adults

The majority of subjects in the 12 to 18 year old age group received the standard adult regimen of FPV/RTV 700/100 mg BID. Compared to the historical adult population receiving FPV/RTV 700/100 mg BID, 12 to 18 year old subjects had 20 % lower plasma APV $AUC_{0-\tau}$, 23 % lower C_{max}, and 20 % lower C_{τ} values. Four subjects in the 12 to 18 year old age group received the FPV oral suspension at a dose of FPV/RTV 15/3 mg/kg BID and plasma APV $AUC_{0-\tau}$ was 41 % lower, C_{max} was 30 % lower, and C_{τ} 33 % lower than observed in the historical adult population.

Reviewer's Comments/Notes Regarding Dose Selection

Dose Selection in 2-5 Year Old Subjects

FPV 30 mg/kg BID and FPV 40 mg/kg BID regimens were both tested in 2 to 5 year old subjects in order to define a dosage regimen that would deliver plasma APV exposures similar to those observed in historical adults receiving FPV 1400 mg BID. Initially, a FPV 40 mg/kg BID dosage regimen was selected for study, but plasma APV exposures were higher than historically observed in adults. Therefore, a FPV 30 mg/kg BID dosage regimen was subsequently selected for study in an additional group of subjects. The FPV

30 mg/kg BID regimen delivered exposures consistent with adults, with a 11 % lower $AUC_{0-\tau}$, similar C_{max}, and 28 % higher C_τ values observed in the 2 to 5 year old subjects compared to the historical adult population. ***Based on the exposure comparisons, the dose selected (30 mg/kg FPV) in pediatric subjects 2-5 years of age, is appropriate.***

Dose Selection in 6-11 Year Old Subjects

FPV/RTV 15/3mg/kg BID and FPV/RTV 18/3mg/kg BID regimens were both evaluated in 6 to 11 year old subjects in order to define a dosage regimen that would deliver plasma APV exposures similar to those observed in historical adults receiving FPV/RTV 700/100 mg BID. Initially, a FPV/RTV 15/3mg/kg BID dosage regimen was selected for study, but preliminary data suggested that plasma APV exposures were slightly lower; therefore a FPV/RTV 18/3mg/kg BID regimen was selected for study in an additional group of subjects. The FPV/RTV 18/3mg/kg BID regimen delivered exposures consistent with adult values, with a 26 % higher $AUC_{0-\tau}$ and similar C_{max} and Cτ values observed in the 6 to 11 year old subjects compared to the historical adult population. The standard adult FPV/RTV 700/100mg BID regimen was administered to three 6 to 11 year old subjects and also delivered exposures consistent with adult values. ***Based on the exposure comparisons, the dose selected (18/3 mg/kg FPV/RTV b.i.d.) in pediatric subjects 6-11 years of age, is appropriate.***

Dose Selection in 12-18 Year Old Subjects

The standard adult FPV/RTV 700/100mg BID regimen was studied in 12 to 18 year old subjects and plasma APV exposures were approximately 20 % lower than observed in the historical adult population receiving the same regimen. However, there was overlap in the exposures observed in the 12-18 year old subjects in this study and the historical adult exposures. Therefore, the decrease in exposure (20 %) is not likely to be of clinical concern. ***Based on the exposure comparisons, the dose selected in subjects 12-18 years of age (FPV/RTV 700/100mg BID) is appropriate.***

12. Conclusion

- In subjects 2-5 years old, administration of FPV 30 mg/kg BID provided exposures similar to historical adult exposures after administration of 1400 mg BID
- In subjects 6-11 years old, administration of 18/3 mg/kg BID provided exposures similar to historical adult exposures after administration of 700/100 mg BID.
- The 12-18 year old subjects receiving the standard adult regimen of 700/100 mg BID showed lower (~20-23 % for C_{max}, AUC, and C_τ) exposures than adult exposures, however, these lower exposures are not expected to be of clinical concern.

4.2 OCPB Filing/Review Form

General Information About the Submission			
	Information		Information
NDA Number	**22-116**	**Brand Name**	**Lexiva**
OCP Division	**DCP 4**	**Generic Name**	**Fosamprenavir**
Medical Division	**DAVP**	**Drug Class**	**HIV Protease Inhibitor**
OCP Reviewer	**Vikram Arya**	**Indication(s)**	**HIV-1 Infection**
OCP Team Leader	**Kellie Reynolds**	**Dosage Form**	**Suspension (50 mg/mL) and Tablet (300 mg)**
		Dosing Regimen (Approved in Adults)	**1400 mg BID 1400 mg QD + RTV 200 mg QD 700 mg BID + RTV 100 mg BID**
Date of Submission	**December 13, 2006**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**GlaxoSmithKline**
PDUFA Due Date	**June 13, 2007**	**Priority Classification**	**Priority Review**
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	2		
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2		
Bioequivalence studies -				
traditional design; single / multi dose:				

replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Vikram Arya
6/14/2007 10:42:24 AM
BIOPHARMACEUTICS

Kellie Reynolds
6/14/2007 10:50:34 AM
BIOPHARMACEUTICS