CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-116

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
NDA 22-116; SN 000, Review Completed 05/29/07

Reviewer: LALJI MISHRA, Ph.D.
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Sponsor: GlaxoSmithKline
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Product Names:

a. Proprietary: Lexiva^{R}
b. Non-proprietary: Fosamprenavir calcium
c. Chemical: (3S)-tetrahydrofuran-3-yl (1S, 2R)-3-[[(4-aminophenyl) sulphonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt

Indication: Treatment of HIV-1 infection in combination with other antiretroviral drugs
Route of Administration/Dosage Form: Oral/Tablet

BACKGROUND:

Glaxo Smith Kline (GSK) has submitted a new drug application NDA # 22-116 for Lexiva^{R} (fosamprenavir calcium) and seeks marketing approval of 50 mg/mL oral suspension of Lexiva for the treatment of HIV-1 infected pediatric patient's ages 2 years to 18 years of age. In addition, GSK seeks appropriate direction for use of Lexiva oral suspension and tablets in HIV-1 infected pediatric patients and patients with hepatic impairment. Fosamprenavir tablet was approved on October 20, 2003. The sponsor has cross-referred to NDA 21-548 and NDA 21-007. Microbiology data for fosamprenavir have been reviewed previously (Microbiology review of NDA 21-548 dated 09/25/2003) and subsequent phase 4 marketing commitments (NDA 21-548, SN 000 (4F), dated 08/10/05).

Fosamprenavir (FPV), also referred to as GW433908, is a calcium phosphate ester prodrug of amprenavir (APV), an inhibitor of the HIV-1 protease. FPV is hydrolyzed by cellular alkaline phosphatase to APV and inorganic phosphate in vivo. APV is primarily the form detected in plasma following administration of FPV. APV exhibits anti-HIV-1 activity both in cell culture and in vivo. The anti-HIV-1 activity of APV varied with host cell types, multiplicity of infection and assay conditions used. The EC_{50} values of APV against HIV-1_{IIIB} ranged from 0.012 to 0.41 μM. The EC_{50} values of APV against HIV-1 clinical isolates (n=9) ranged from 0.0008 to 0.0380 μM (Microbiology review of NDA 21-548; dated 09/25/03).

The median EC_{50} value of APV against HIV-1 isolates from clades A to G was 0.00095 μM in peripheral blood mononuclear cells (PBMCs). Similarly, the EC_{50} values for APV

against monocytes/macrophage tropic HIV-1 isolates (clade B) ranged from 0.003 to 0.075 μM in monocyte/macrophage cultures. The EC_{50} values of APV against HIV-2 isolates grown in PBMCs were higher than those for HIV-1 isolates, and ranged from 0.003 to 0.11 μM. APV exhibited synergistic anti-HIV-1 activity in combination with the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine and efavirenz; the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir (ABC), didanosine, lamivudine (3TC), stavudine, tenofovir, and zidovudine; and the protease inhibitors (PIs) atazanavir (ATV) and saquinavir (SQV). APV exhibited additive anti-HIV-1 activity in cell culture in combination with the NNRTI nevirapine, the PIs indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), and ritonavir (RTV); and the fusion inhibitor enfuvirtide.

Resistance analysis data for studies APV 30001, 30002, 30003, and APV30005 were reviewed earlier (Microbiology review of original NDA 21-548 dated 09/25/03 and NDA 21-548, SN-000 (4F), dated 08/10/05). In study APV 30001, 166 antiretroviral naïve patients were treated with FPV in combination with ABC and 3TC. Genotypic analysis of baseline-matched on-therapy HIV-1 isolates from 29 patients with virologic failure (plasma HIV-1 RNA of ≥1,000 copies/mL on two consecutive occasions on or after Week 12 treatment) on FPV therapy showed that isolates from 5/29 contained APV-resistance-associated amino acid substitutions I54L/M (n=2), I54L + L33F (n=1), V32I + I47V (n=1) and M46I + I47V (n=1).

Genotypic analysis showed that none of the baseline matched on-therapy HIV-1 isolates from patients with virologic failure (n=32) in study APV 30002 (n=322) contained any mutation associated with resistance to APV at week 48. However, the on-therapy isolate from one patient contained an I54V mutation.

In study APV 30003, two doses of FPV plus low dose RTV in combination with 2 NRTIs were administered. Virologic failure patients with prior experience with one or two PIs were randomized to FPV/RTV QD (n=105), FPV/RTV BID (n=107) or LPV/RTV BID (n=103) treatment groups. Only data relevant to FPV/RTV QD and FPV/RTV BID are cited here. The majority of patients had received prior treatment with IDV, NFV or SQV (with or without RTV). No patient had previously received APV or LPV. The primary PI resistance-associated mutations in baseline HIV-1 isolates of patients from each treatment group were L90M, M46I/L, D30N, V82A/F/T/S, N88D, I54V, I84V, N88S, G48V, V32I, I54L, and I47V, in decreasing order of occurrence. Mutations D30N, N88D/S and L90 M are associated with NFV resistance (Shafer 2002; Stanford University Resistance Database 2002). The I54V, V82A/F/T/S mutations are associated with resistance to IDV and RTV (Molla et al.,1996). Mutations G48V and L90M are associated with resistance to SQV. Mutations V32I, M46I/L, I 47V, I54L, I84V are associated with APV resistance. V32I also develops in concert with V82A mutation in HIV-1 isolates from patients treated with IDV. The I54V mutation, associated with resistance to APV, IDV, LPV, RTV, and SQV, was present in baseline HIV-1 isolates from 12/105, and 11/107 patients receiving FPV/RTV QD and FPV/RTV BID,

respectively. The I54L mutation, associated with APV resistance, was detected in baseline isolates from 2/107 patients randomized to FPV/RTV BID. The mutation I84V, which is associated with resistance to most approved PIs and develops in HIV-1 isolates from patients treated with APV, IDV, RTV and SQV, was present in baseline HIV-1 isolates from 8/105, and 8/107, patients receiving FPV/RTV QD, and FPV/RTV BID, respectively. The APV resistance-associated mutations I50V and I54M were not detected in baseline HIV-1 isolates from any of the patients enrolled in study APV 30003. Genotypic analysis showed that accessory mutations L63P, A71V/T, V77I, L10I/F/V/R and M36I, in decreasing order of prevalence, were present in baseline HIV-1 isolates from most patients.

In APV30005, PI-experienced subjects received FPV 700 mg BID/RTV 100 mg BID. The PI mutations present in baseline isolates were reviewed earlier (Please see Microbiology review of NDA 21-548). Like APV 30003 study, the effect of baseline PI-mutations on virologic response (responder <400 copies/mL and virologic failure ≥400 copies/mL) at Wk 96 was analyzed. Similar to virologic response at Wk 48, baseline mutations D30N and N88D had no major effect on virologic response (< 400 copies/mL) at Wk 96. However, baseline mutations M46I/L, V82A/F/T/S, I84V and L90M either alone or in concert affected the virologic response at Wk 96 in patients receiving FPV/RTV BID. These results are in agreements with virologic response for FPV/RTV BID treatment group at Wk 48. The baseline mutation I84V had significant effect on virologic response at Wk 96.

In support of this NDA, GSK has submitted 48 weeks data for studies APV20003, APV 29005 and APV 20002. APV20003 and 20095 are pivotal studies for dose selection for patients 2 to 18 years of age and APV 20002 is a supportive study. Microbiology data for these studies are reviewed here.

Study APV 20003

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/Ritonavir BID when Administered to HIV-1 Infected, Antiretroviral Naive and Experienced, Pediatric Subjects 2 to 18 Years Old.

OBJECTIVES

Primary

1. To evaluate the safety and tolerability of FPV/RTV given once daily in combination with NRTI therapy for 48 weeks in HIV-1 infected antiretroviral therapy(ART)-naïve and experienced, pediatric subjects 2 to ≤18 years of age.
2. To characterize plasma APV PK following administration of FPV/RTV once daily and twice daily to pediatric subjects 2 to ≤18 years of age.

Secondary

1. To assess whether FPV has systemic exposure when administered to HIV-1 infected pediatric subjects 2 to ≤18 years of age.
2. To investigate the relationship of plasma APV PK to changes in plasma HIV-1 RNA concentrations, $CD4^+$ cell counts and to the occurrence of adverse events (AEs).
3. To assess viral resistance patterns and to compare these patterns with treatment outcome.
4. To assess subject adherence, shaking of FPV oral suspension and parent/guardian perceptions of study medications.
5. To evaluate the antiviral activity of FPV/RTV administered once daily in combination with NRTI therapy for 48 weeks in HIV-1 infected, antiretroviral therapy-naïve and experienced pediatric subjects 2 to ≤18 years of age.
6. To evaluate the immunologic activity of FPV/RTV administered once daily with NRTI therapy for 48 weeks in HIV-1 infected, antiretroviral therapy-naïve and experienced pediatric subjects 2 to ≤18 years of age as determined by changes in $CD4^+$ cell count.
7. To evaluate the safety, tolerability, antiviral activity, immunologic response and adherence of subjects who switch to a FPV/RTV BID regimen after initially receiving a FPV/RTV QD regimen.

Microbiologic Specific Inclusion Criteria

A subject was eligible for inclusion in this study only if all of the following criteria applied:

1. Male or females 2 to ≤18 years of age.
2. Plasma HIV-1 RNA ≥400 copies/mL.
3. Subject must meet one of the following criteria:
   - ART-naïve subjects were defined as having had ≤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. PI-experienced subjects were eligible if they had previously been treated with ≤3 PIs, excluding AGENERASE. Prior therapy with a RTV boosted PI regimen was considered as only 1 prior PI as long as the RTV dose was below recommended dose for use of RTV as an antiretroviral agent.

Microbiologic Specific Exclusion Criteria

A subject was not eligible for inclusion in the study if any of the following criteria applied:

1. Prior history of having received APV.

2. Non-nucleoside reverse transcriptase inhibitor therapy within 14 days prior to study drug administration or anticipated need for concurrent NNRTI therapy during the study period.
3. Treatment with immunomodulating agents (e.g., systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (e.g., hydroxyurea or foscarnet) within 28 days of study drug administration.
4. Systemic cytotoxic chemotherapy.
5. Treatment with other investigational drugs/therapies within 28 days prior to study drug administration.
6. History of drug or other allergy which in the opinion of the investigator contraindicates participation in the trial or known hypersensitivity to any study medications (e.g., documented hypersensitivity to a nucleoside analogue).

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. This study was performed at study centers in North America and in Europe. Subjects that successfully completed 48 weeks of therapy in this study continued to receive FPV until commercial supplies of FPV became available locally. Enrolment was initially open to Cohorts 1 (2 to <6 years), 2 (6 to <12 years) and 3 (12 to 18 years) and occurred in parallel. Subjects were either ART-naïve or ART-experienced. Once enrolment in any given Cohort (1, 2 or 3) was complete, further subjects in that age range started enrolling in Cohort 4 (2 to 18 years).

Dosage and Administration

FPV Regimen

FPV/RTV QD

FPV was administered as either oral 700 mg tablets (600 mg APV molar equivalents) or 50 mg/mL oral suspension (43.2 mg/mL APV molar equivalents). RTV was given as either an 80 mg/mL oral solution, or 100 mg capsules.

ABC and 3TC were supplied in their own bottles in both the oral liquid formulations and the tablet formulations. ABC oral solution was provided as a 20 mg/mL oral solution and the ABC 300 mg tablets. 3TC was supplied as a 10 mg/mL oral solution and the 150 mg tablets.

FPV 700 mg tablets were available to subjects who were at least 12 years of age, weighed ≥50 kg 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 1400 mg QD in combination with RTV 200 mg QD. RTV 100 mg capsules were made available to

subjects who weigh ≥33 kg and who were able to swallow whole capsules, at the discretion of the investigator.

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 until Week 4 PK data was available from at least 6 subjects in the cohort. These individual FPV dosage regimen adjustments were made to ensure that target plasma APV concentrations were achieved.

Target plasma APV exposure for subjects receiving a FPV/RTV QD regimen was defined as a plasma APV Cτ value of ≥1.02 μg/mL. This target represented the 25th percentile observed in adult subjects receiving AGENERASE 1200mg QD + RTV 200mg QD in APV20001.

FPV/RTV BID dose adjustments based on Week 4 PK Assessments

Similar to the FPV/RTV QD regimen, individualized FPV dosage regimen adjustments were permitted for subjects receiving the FPV oral suspension, based on their Week 4 plasma APV PK data to ensure that target plasma APV concentrations were achieved. Target plasma APV exposure for subjects receiving a FPV/RTV BID regimen was defined as a plasma APV Cτ value of ≥1.48 μg/mL. This target represented the 25th percentile observed in adult subjects receiving FPV 700 mg BID + RTV 100mg BID in APV10010, APV10011, APV10012, APV10013, and APV10022.

Virological Failure Population

Plasma samples for HIV Resistance Testing (Geneseq and Phenosense™, Monogram Biosciences, Inc.) were taken from subjects with plasma HIV-1 RNA >400 copies/mL at Week 24/48 together with the baseline samples for these subjects. In addition, samples with plasma HIV-1 RNA >400 copies/mL were taken at other time points during the study at the investigators request to aid patient management.

I. Baseline characteristics of subjects enrolled in study APV20003

A total of 69 subjects were enrolled in study APV20003. The median plasma HIV-1 RNA ($\log_{10}$ copies/mL) and the $CD4^+$ cell count for these subjects at baseline are shown in Table 1. The median plasma HIV-1 RNA for subjects 2 to 5 years, 6 to 11 years and 12 to 18 years age were similar; 4.8, 4.8 and 4.9 $\log_{10}$ copies/mL, respectively. A majority of subjects (54/69) in these 3 age groups had HIV-1 plasma RNA of 5,000 to 500,000 copies/mL (3.69 to 5.69 $\log_{10}$ copies/mL) at baseline. However, the median $CD4^+$ cell counts were higher in age group 2 to 5 years than those in 6 to 11 and 12 to 18 years age group, respectively. The median $CD4^+$ cell counts for age groups 2 to 5 years, 6 to 11 years and 12 to 18 years were 853, 387 and 283, respectively.

Table 1: median plasma HIV-1 RNA values and $CD4^+$ cell counts for subjects enrolled into study APV20003 ITT(E) population at baseline (Source NDA 22-116, GSK study report RM2004/00512/01, Page 72, Table 9)

	2-5 Years N=17	6-11 Years N=17	12-18 Years N=35	FPV/RTV N=69
Baseline HIV-1 RNA				
Median plasma HIV-1 RNA log_{10} copies/mL, (IQR)	4.8 (4.3, 5.2)	4.8 (4.3, 5.2)	4.9 (4.2, 5.3)	4.8 (4.3, 5.2)
HIV-1 RNA copies/mL, n (%)				
<400	1 (6)	0	1 (3)	2 (3)
400 – <5000	2 (12)	1 (6)	3 (9)	6 (9)
5000 – <100,000	8 (47)	10 (59)	16 (46)	34 (49)
100,000 – 250,000	2 (12)	3 (18)	10 (29)	15 (22)
>250,000 – 500,000	1 (6)	2 (12)	2 (6)	5 (7)
≥500,000	3 (18)	1 (6)	3 (9)	7 (10)
Baseline CD4+ cell counts (absolute)				
Median CD4+ cells/mm^3 (IQR)	853 (675,1218)	387 (287, 654)	283 (141, 388)	370 (260, 675)
CD4+ cells/mm^3, n (%)				
<100	0	2 (12)	7 (20)	9 (13)
100 – <200	0	1(6)	4 (11)	5 (7)
200 – <350	1(6)	4 (24)	12 (34)	17 (25)
350 - <500	3 (18)	4 (24)	7 (20)	14 (20)
≥ 500	13 (76)	6 (35)	5 (14)	24 (35)

II. Subjects with prior PI antiretroviral therapy

The number of subjects with prior PI antiretroviral therapy is summarized for the ITT (E) population in Table 2

Table 2: Summary of prior PI antiretroviral therapy in the PI-experienced subjects in the study APV20003 ITT (E) population (Source: NDA 22-116, GSK study report RM2004/00512/01, Page 75, Table 12)

No of PI taken	Total N=37
1	22 (59)
2	11 (30)
3	4 (11)
PIs taken	

IDV	10 (27)
IDV + RTV	1 (3)
Kaletra™	4 (11)
NFV	22 (59)
NFV + RTV	1 (3)
RTV	15 (41)
SQV	2 (5)
SQV + RTV	1 (3)
Median duration of all PI exposure	
Median (range)	148 (3, 291)

Table 2 shows that most PI-experienced subjects enrolled (59%, 22/37) had one prior PI-exposure with only 4 enrolled subjects had 3 prior PI-exposures. The median duration of prior PI exposure was 148 weeks. A majority of subjects had received NFV, followed by RTV or IDV.

III. Effect of FPV/RTV treatment on virologic response

Plasma HIV-1 RNA levels were quantified at baseline, Weeks 2, 4, 8, 12, 24, and 48 using Roche Amplicor HIV-1 Monitor™ Test;(Ultrasensitive , version 1.5, lower limit of quantification (LLOQ) = 50 copies/mL). Samples with >75,000 copies/mL were retested using the Roche Amplicor HIV-1 Monitor™ Test (standard, LLOQ= 400 copies/mL). The median HIV-1 RNA levels and median change from baseline in HIV-1 RNA levels by PI status and visit for in the ITT (E) population observed are presented in Table 4 and Table 5.

Table 4: Median plasma HIV-1 RNA 1 by visit and PI Status in APV20003 ITT (E) population (Source: NDA 22-116, GSK study report RM 2004/00512/01, Page 78, Table 16)

	Plasma HIV-1 RNA (log_{10} copies/mL) Median [IQR]			
Week	PI-naive N=32	N	PI-experienced N=37	n
Baseline	4.72 [4.29, 5.22]	32	4.88 [4.32, 5.18]	37
Week 2	3.02 [2.46, 3.41]	26	3.26 [2.41, 3.51]	34
Week 4	2.66 [2.08, 2.90]	28	2.91 [1.97, 3.34]	34
Week 8	2.01 [1.73, 2.39]	28	2.52 [1.69, 4.15]	32
Week 12	1.69 [1.69, 1.97]	26	1.83 [1.69, 4.08]	32
Week 24	1.69 [1.69, 2.67]	26	2.09 [1.69, 3.98]	34
Week 48	1.69 [1.69, 2.63]	21	1.69 [1.69, 3.97]	25

Table 4 shows that at Week 48, 21/32 prior PI-naïve and 25/37 prior PI-experienced subjects achieved the median plasma HIV-1 RNA levels of ≤50 copies/mL, the lower limit of assay quantification (1.69 log_{10} copies/mL). The median decrease of plasma HIV-1 RNA levels from baseline was 2.65 log_{10} copies/mL in prior PI-naïve group and 1.65 log_{10} copies/mL in prior PI-experienced group (NDA 22-116, study APV 20003, GSK study report RM 2004/00512/01, Page 78, Table 17).

IV. **Summary of study outcome at week 48 in study APV 20003**

In the TLOVR analysis for the ITT (E) population, the proportion of subjects with plasma HIV-1 RNA <400 copies/mL at Week 48 was 47% in the PI-naïve group and 43% in the PI-experienced group. Table 5 shows the summary of study outcome using the TLOVR analysis in the ITT (E) population.

Table 5: Summary of study outcome at week 48 in study APV20003 (Source: NDA 22-116, study APV 20003, GSK study report RM 2004/00512/01, Page 81, Table 20).

Outcome	PI-naive N=32 n (%)	PI-experienced N=37 n (%)	Total N=69 n (%)
Responders (<400copies/mL plasma HIV-1 RNA)	15 (47)	16 (43)	31 (45)
Primary reason for failure (non-responders)			
Virological failure	9 (28)	11 (30)	20 (29)
Plasma HIV-1 RNA rebound	8 (25)	4 (11)	12 (17)
Never achieved viral load suppression through Week 48	1 (3)	5 (14)	6 (9)
Insufficient viral load response	0	2 (5)	2 (3)
Discontinued study drug before achieving suppression	5 (16)	8 (22)	13 (19)
Due to an adverse event	3 (9)	2 (5)	5 (7)
Due to consent withdrawn	1 (3)	1 (3)	2 (3)
Due to other reason	1 (3)	5 (14)	6 (9)
Discontinued study drug while suppressed	3 (9)	2 (5)	5 (7)
Due to an adverse event	1 (3)	2 (5)	3 (4)
Due to other reasons	1 (3)	0	1 (1)
Missing HIV-1 RNA data at Week 48	1 (3)	0	1 (3)

Table 5 shows that 20 subjects were virologic failure. The major reason for virologic failure in the PI-naïve study population was due to a plasma HIV-1 rebound, whereas in the PI-experienced study population, the primary reasons for virologic failure were plasma HIV-1 rebound and never achieving viral load suppression by Week 48.

Comment

TLOVR analysis considered showed 20 subjects as virologic failure. TLOVR analysis uses only data up to Week 48 and requires viral load to be confirmed above >400 copies/mL to meet definition of virologic failure. However, for resistance analysis 30 subjects were grouped as virologic failure (>400 copies/mL HIV-1 RNA) at Week 24 and/or Week 48 and other time points on investigator's requests.

VI. Genotypes of baseline matched on-therapy isolates from virologic failure subjects

Genotypes of baseline matched on-therapy HIV-1 isolates from subjects with HIV-1 RNA >400 copies/mL at Week 24 and/or Week 48 were determined using Genseq methods. Additionally genotypes of isolates were determined from subjects during weeks 4-108 by investigators.

VI (a). Genotypes of baseline matched on-therapy isolates from virologic failure subject with emerging APV resistance-associated mutations during therapy

The genotypes of baseline matched on therapy isolates with emerging APV-resistance associated mutation are shown in Table 6.

Table 6: Genotypes of isolates from virologic failure subjects at Week 24 and/or Week 48 (Source: NDA 22-116, GSK study report RM2004/00512/01, Pages 137-139, Table 64)

Subject ID *	Visit	Plasma HIV-1 RNA (copies/mL)	PR mutation	RT mutation
6353 PI-exp	Day1	15,000		
	Week 24	1200		
	Week 36	350		
6453 PI-naïve	Day 1	95,000		
	Week 24	650		
	Week 48	4100		
	Week 96	9070		
6492 PI-exp	Day 1	50,000		
	Week 12	34,000		
	Week 24	10,000		
	Week 48	27,000		
6994 PI-exp	Day1	>75,000		
	Week 24	67,000		
7256 PI-exp	Day1	150,000		
	Week 24	12,000		
	Week 48	38,000		

b(4)

Mutations in bold emerged during therapy.
* subjects # 6353, and 6492 were 6-11 years old; all other subjects listed in Table 6 were 12-18 years old.
All subjects received FPV/RTV QD.

Table 6 shows that on-therapy isolates from isolates 5 subjects (# 6353, 6453, 6492, 6994 and 7256) developed APV resistance-associated mutations L33F, I50V, I54L during therapy. Four of these subjects were PI-experienced prior to enrollment into the study APV20003 and one subject (# 6453) was PI-naïve.

VI (b). Genotypes of baseline matched on-therapy isolates from virologic failure subjects which did not develop APV resistance-associated mutations during therapy

Genotypes of baseline matched on-therapy isolates from virologic failure subjects which did not develop APV resistance associated mutations and maintained baseline PR mutations are shown in Table 7.

Table 7: Genotypes of isolates from virologic failure subjects at Week 24 and/or Week 48 with baseline PR mutations and no new emergent mutations during therapy (Source: NDA 2216, GSK study report RM2004/00512/01, Pages 137-139, Table 64)

Subject ID*	Visit	Plasma HIV-1 RNA (copies/mL)	PR mutations
6312 PI-exp	Day 1	310,000	b(4)
	Week 48	9300	
6333 PI-exp	Day 1	150,000	
	Week 60	3300	
6433 PI-exp	Day 1	10,000	
	Week 48	990	
6479 PI-naïve	Day1	94,000	
	Week 48	4140	
6989 PI-naïve	Day 1	38,000	
	Week 24	64,000	
7012 PI-exp	Day1	21,000	
	Week 24	8200	
7026 PI-exp	Day 1	21,000	
	Week 48	11,000	
7059 PI-exp	Day1	11,000	
	Week 24	63,000	
7061 PI-exp	Day 1	190,000	
	Week 24	190,000	

*Subject # 6333 and 7012 were 6-11 years old, all other subjects were 12-18years old.
All subjects received FPV/RTV QD.

VI (c). Genotypes of baseline matched on-therapy isolates from virologic failure subjects with no mutations associated with protease resistance during therapy

Table 8 shows that baseline and on therapy isolates from two PI naïve subjects did not contain any mutations associated with protease (PR) resistance.

Table 8: Genotypes of baseline matched on-therapy isolates from virologic failure subjects with no PR resistance-associated mutations (Source: NDA 22-116, GSK study report RM2004/00512/01, Pages 137-139, Table 64)

Subject ID*	Visit	Plasma HIV-1 RNA (copies/mL)	PR mutations
6495 PI-naïve	Day1	13,000	None
	Week 24	470	None
7029 PI-naïve	Day 1	65,000	None
	Week 24	500	None

Subject # 6495 was 12-18 years old and subject # 7029 was 2-5 years old.

Results presented in Tables 6, 7 and 8 showed that genotypes of baseline matched on-therapy isolates were available from 16 virologic failure subjects. Of these, on-therapy isolates from 5 subjects developed APV-resistance associated mutations during therapy. Protease resistance mutations present in baseline isolates were maintained in on -therapy isolates from these subjects. However, no new mutation developed during therapy in on-therapy isolates from 9 other subjects. Additionally, both baseline and on-therapy isolates from 2 PI-naïve subjects did not contain any mutation associated with PR resistance. This analysis is limited for PR mutations. Like PR mutation, NRTI resistance-associated mutations also caused virologic failure.

VII. Genotypes of baseline and on-therapy isolates from subjects selected by the Investigators

On-therapy and screen samples from 12 subjects selected by the investigators during therapy (Week 8 to Week 108) were genotyped. Nine of the 12 subjects were PI-experienced and 3 were PI-naive. On-therapy isolates from most subjects maintained protease resistance associated mutations present at screen (Table 9). However, on-therapy isolates from 3 subjects (# 6424, 7027 and 7053) developed APV-resistance associated mutations I47V, I50V, I54L/M and I84V during therapy.

Table 9: Genotypes of screen (baseline) matched on therapy isolates from virologic failure subjects samples collected during Week 8 to Week 108 (Source: NDA 22-116, GSK study report RM2004/00512/01, Pages 141-142, Table 65)

Subject ID	Visit	Plasma HIV-1 RNA(copies/mL)	PR mutations
6314 PI-exp	Screen	200,000	
	Week 16	110,000	
6338 PI-exp	Screen	59,000	
	Week 48	21,000	
6352 PI-naive	Screen	790,000	
	Week 72	9,7000	
6422 PI-exp	Screen	>750,000	
	Week 8	640,000	
6424 PI-exp	Screen	48,000	
	Week 48	310,000	
6512 PI-exp	Screen	810,000	
	Week 16	1,700	
6982 PI-exp	Screen	48,000	
	Week 108	6,000	
6983 PI-exp	Screen	560,000	
	Week 96	150,000	
6992 PI-naive	Day 1	100,000	
	Week 48	48,000	
7027 PI-exp	Screen	89,000	
	Week 48	7400	
7052 PI-naive	Screen	97,000	
	Week 84	45,700	
7053 PI-exp	Screen	78,000	
	Week 48	19,000	

b(4)

Bold represents new mutations
*= Subject # 6352, 6983,7053 were 2-5 years old, subject #s 6338, 6422, 6982, 7052 were 6-11 years old and all other subjects were 12-18 years old.
All subjects received FPV/RTV QD.

VIII. Phenotypic analysis of baseline and on therapy isolates from virologic failure subjects.

Susceptibility of baseline and on-therapy isolates to APV was determined using Phenosence ™ assay (Monogram Biosciences, Inc., San Francisco, CA). Results from phenotypic analysis are shown in Table 10

Table 10: Phenotypic analysis (fold change) of baseline and on-therapy isolates from virologic failure subjects (Source: NDA 2216, GSK study report RM2004/00512/01, Pages 145-146, Table 67)

Subject ID	Visit	PI therapy	Fold resistance
6353	Day1	APV	1.93
	Week 24	APV	4.19
	Week36	APV	5.19
6453	Day 1	APV	0.68
	Week 24	APV	0.76
	Week 48	APV	1.44
	Week 96	APV	9.22
6492	Day 1	APV	3.51
	Week 12	APV	5.4
	Week 24	APV	12.0
	Week 48	APV	17.0
6994	Day1	APV	3.2
	Week 24	APV	38.0
7012	Day 1	APV	3.02
	Week 24	APV	4.42
7059	Day 1	APV	1.63
	Week 24	APV	4.03
7256	Day 1	APV	0.92
	Week 48	APV	4.41

Resistance to APV (arbitrarily set at >2.0 fold the biological cut-off) was observed in baseline isolates from 3 subjects. Baseline isolates from subject # 6492 with I84V substitution, subject 6994 with primary mutation V82A/T and subject # 7012 with primary mutation L90M exhibited 3.5, 3.2 and 3.02-fold resistance to APV, respectively. On-therapy isolates from subject # 6492 and # 6994 exhibited 17, and 38-fold resistance to APV. On-therapy isolates from subject # 7012 exhibited 4.43-fold resistance to APV. Additionally, on therapy isolates from subject # 7059 and 7256 exhibited 4.03- and 4.91-fold resistance to APV. On-therapy isolates from subject #7059 contained resistance-associated substitutions L10F, D30N, M36I, L63P V77I and N88D mutations. On the other hand, on-therapy isolates from subject # 7256 developed APV-resistance associated substitutions, L33F and I54L.

On-therapy isolates from subject t# 6353 developed substitutions L33F, A71T and L90M during therapy and exhibited 4.19 and 5.19-fold resistance to APV at weeks 24 and 36, respectively. Both baseline and on-therapy isolates from subject # 7012 exhibited 3.02 to 4. 42-fold resistance to APV and contained substitutions L10V, M36I, L63P, A71I/T/V and L90M.

For the investigator requested subjects, samples for baseline phenotypic analysis were not available for comparison except for the subject # 6992. On therapy isolates from 4 subjects (#6338, 6424, 7027, 7053) exhibited 2.24 to 12.0-fold resistance to APV at Week 48 (NDA 22-116, GSK study report RM2004/00512/01, Page 147, Table 68).

Isolates from 3 of these 4 subjects (# 6424, 7027,7053) developed APV-resistance-associated substitutions (I47V, I54L/M, I84V) during therapy. On-therapy isolates from subject 6338 exhibited 2.24-fold resistance to APV and both baseline and on-therapy isolates contained APV resistance-associated substitution I54V in combination with substitutions L10I, L63P, A71T and V82A (NDA 22-116, GSK study report RM2004/00512/01, Page 141, Table 65).

The phenotypes of baseline and on-therapy isolates correlated with genotypes.

XI. Cross-resistance of on-therapy isolates to PIs (IDV, LPV, NFV, RTV, SQV

A summary of PI cross-resistance for isolates showing APV resistance together with genotypes are shown in Table 11. On-therapy and baseline isolates (where available) from 11 subjects with APV resistance associated mutations were tested for susceptibility to IDV, LPV, NFV, RTV, and SQV. The number of mutations associated with PI resistance and a combination of major PI mutations exhibited different degrees of cross-resistance. Most APV resistant isolates were cross-resistant to IDV, NFV, RTV and SQV depending on the number of mutations and a particular mutation in the protease gene. For example a combination of I54L/M and I84V present in on-therapy isolates from subject # 6492 conferred cross-resistance to most PIs tested. Similarly, on-therapy isolates harboring I54L/M mutation in combination with V82A conferred cross resistance to IDV, LPV NFV, RTV, and SQV (subject # 6338, 6994). In general most APV resistant isolates were cross-resistant to IDV, RTV and SQV. On the other hand, baseline and on-therapy isolates from most subjects were susceptible to LPV (Table 11).

Table 11: Cross-resistance of APV resistant baseline and on-therapy isolates to other PIs (Source: NDA 22-116, GSK study report RM2004/00512/01, Pages 147-148, Table 69)

Subject ID	Visit Description	Genotypes	Phenotype*					
			APV	IDV	LPV	NFV	RTV	SQV
6338	Week 48	[redacted]	2.24	8.57	12.0	9.41	28.0	1.87
6353	Week 24		4.19	4.37	4.84	23.0	21.0	6.45
	Week 36		5.19	3.24	3.81	16.0	23.0	7.72
6424	Week 48		12.0	3.27	6.07	7.05	11.0	2.83
6453	Week 96		9.22	1.17	3.01	4.60	9.52	1.78
6492	Day 1		3.51	2.33	9.81	2.75	16.0	1.4
	Week 12		5.4	4.10	20.0	3.80	19.0	3.90
	Week 24		12.0	4.56	36.0	6.8	27.0	9.62
	Week 48		17.0	2.98	17.0	5.83	20.0	8.01
6994	Day 1		3.2	5.4	9.02	6.82	20.0	1.52
	Week 24		38.0	2.00	36.0	2.51	82.0	1.23
7012	Day 1		3.02	6.56	2.91	38.0	14.0	8.31
	Week 24		4.42	7.90	2.90	43.0	15.00	10.0
7027	Week 48		11.0	4.75	6.70	3.30	8.98	1.59
7053	Week 48		5.03	0.79	2.05	1.91	3.82	2.10
7059	Week 16		3.79	3.03	3.63	67.0	2.04	2.47
	Week 24		4.03	3.12	4.15	83.0	3.26	2.56
7256	Week 48		4.11	1.04	1.53	2.41	2.84	1.57
Number of Subjects with Susceptible virus to each PI			0/11	4/11	8/11	2/11	0/11	3/11

b(4)

– * = In bold if above the susceptibility cut-off, APV=2, IDV=2.5,LPV=10,NFV=2.5, RTV=2.5, SQV=1.7

Study APV29005

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

OBJECTIVES

Primary

1. To define the FPV/RTV BID dosage regimens which will provide target steady-state plasma APV exposure to pediatric subjects 2 to 18 years of age.
2. To evaluate the safety and tolerability of FPV/RTV BID in combination therapy for 48 weeks in HIV-1 infected PI-naïve and PI-experienced pediatric subjects 2 to 18 years of age.
3. To define the FPV BID dosage regimens which will provide target steady-state plasma APV exposure to pediatric subjects 2 to 5 years of age.
4. To evaluate the safety and tolerability of FPV BID in combination therapy for 48 weeks in HIV-1 infected PI-naive pediatric subjects 2 to 5 years of age

Secondary

1. To assess plasma FPV exposure when administered to HIV-1 infected pediatric subjects 2 to 18 years of age.
2. To characterize plasma RTV pharmacokinetics (PK) following administration of FPV/RTV BID to pediatric subjects 2 to 18 years of age.
3. To investigate the relationship of plasma APV PK to changes in plasma HIV-1 RNA concentrations, $CD4^+$ cell counts and to the occurrence of adverse events (AEs).
4. To evaluate the antiviral activity of FPV/RTV BID in combination therapy for 48 weeks in HIV-1 infected PI-naïve and PI-experienced pediatric subjects 2 to 18 years of age and of FPV BID in combination therapy in PI-naïve pediatric subjects 2 to 5 years of age.
5. To evaluate the immunologic activity of FPV/RTV BID in combination therapy for 48 weeks in HIV-1 infected PI-naïve and PI-experienced pediatric subjects 2 to 18 years of age and of FPV BID in combination therapy in PI-naïve pediatric subjects 2 to 5 years of age
6. To assess viral resistance patterns and to compare these patterns with treatment outcome
7. To assess subject adherence to study medications

Endpoints

Primary

1. Plasma APV AUC (0-τ), C_{max}, and Cτ.
2. Proportion of subjects who permanently discontinue FPV/RTV or FPV due to AEs.
3. Incidence and nature of AEs and laboratory abnormalities in study subjects.

Secondary

1. Plasma FPV concentrations.
2. Plasma RTV AUC (0-τ), C_{max}, and Cτ.
3. Correlation of plasma APV PK with plasma HIV-1 RNA concentrations, $CD4^+$ cell counts and to the occurrence of AEs.
4. Proportions of subjects with plasma HIV-1 RNA <400 copies/mL over time
5. Measured values and changes from baseline in plasma HIV-1 RNA over time.
6. Proportion of subjects with $\geq$1.0 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA from baseline over time.
7. Measured values and changes from baseline in $CD4^+$ cell counts over time.
8. Incidence of viral resistance and correlation with outcome.
9. Subject adherence to study medications.
10. Duration of shaking of the FPV oral suspension.

Microbiology Specific Inclusion Criteria

A subject was eligible for inclusion in this study only if all of the following criteria applied:

1. Screening plasma HIV-1 RNA ≥ 400 copies/mL.
2. Subjects met one of the following criteria:
   - ART-naïve or PI-naïve subjects (defined as having received less than 1 week of any PI and any length of therapy with NNRTIs and/or NRTIs).
   - PI-experienced subjects (defined as having received greater than 1 week prior PI therapy with no more than three PIs). Prior RTV boosted PI therapy was considered as only one PI as long as the RTV dose was lower than that recommended for use of RTV as an antiretroviral agent.

Microbiologic Specific Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. Prior history of having received agenerase or FPV for >7 days.
2. NNRTI use within 14 days prior to study drug administration or anticipated need for concurrent NNRTI therapy during the treatment period of the study.
3. Presence of any serious medical condition (e.g., hemoglobinopathy, chronic anemia, a history of insulin resistance, diabetes, cardiac dysfunction, or hepatitis) which, in the opinion of the investigator, compromised the safety of the subject.
4. Grade 3 or 4 transaminase levels (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) within 28 days prior to study drug administration and/or clinically relevant episodes of hepatitis within the previous 6 months.
5. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 28 days of study drug administration or an anticipated need for such treatment within the study period.
6. Treatment with immunomodulating agents (e.g., systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV-1 activity (e.g., hydroxyurea or foscarnet) within 28 days of study drug administration.
7. Treatment with any of the following medications within 28 days prior to receiving study medication or the anticipated need during the study:
   - Drugs whose plasma concentration may be increased to unsafe levels when co-administered with FPV including: amiodarone, astemizole, bepridil, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, halofantrine, lidocaine, lovastatin, methylergonovine, midazolam, pimozide, propafenone, quinidine, simvastatin, terfenadine, and triazolam
   - Drugs with the potential to significantly decrease plasma APV concentrations including: carbamazepine, dexamethasone, phenobarbital, phenytoin, primidone, rifampin, St Johns Wort.
8. Treatment with other investigational drugs/therapies.
9. History of drug or other allergy which, in the opinion of the investigator, contraindicated participation in the trial or known hypersensitivity to any study medications (e.g., documented hypersensitivity to a nucleoside analogue).
10. Substantial non-adherence based on history.

Study Design

APV29005 was an international, 48-week, Phase II, open-label, multi-cohort, multicenter study of HIV-1 infected, PI-naïve and PI-experienced subjects 2 to 18 years old.

This study was conducted at sites in North America, Europe, and Russia. Subjects who successfully completed 48 weeks of therapy in APV29005 were given the opportunity to continue to receive FPV until it is approved and locally available for use in pediatric and adolescent subjects.

Enrolment was initially opened to Cohorts 1A, 1B, 2 and 3 in parallel for all subjects 2 to 18 years of age. Subjects were assigned to a cohort based on age and PI-experience. Cohort 1A was only open to PI-naïve subjects. Cohorts 1B, 2 and 3 were open to either PI-naïve or PI-experienced subjects. Once enrolment in a given cohort (1A, 1B, 2 or 3) was complete, and providing sufficient PK data were available, further subjects in that age range were to enroll in Cohort 4 if recruitment to that specific age range was still open.

Drug Dosing

The first 6 to 10 subjects in each cohort initiated a FPV BID or FPV/RTV BID dosage regimen based on previous APV and FPV pediatric studies.

Cohort 1A (2 to 5 years, FPV BID) subjects initiated dosing with FPV 40 mg/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 this regimen.

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

Cohort 2 (6 to 11 years, FPV/RTV BID) subjects initiated dosing with FPV/RTV 15/3 mg/kg BID. Steady-state PK data from the first eight subjects indicated a cohort dose revision to FPV/RTV 18/3 mg/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 were 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 has been implemented.

X. <u>Baseline characteristics of subjects enrolled in study APV29005.</u>

Several different clades were represented in the enrolled subjects including 25 non-clade B viruses. The main clade represented was clade B, which was the most prevalent in the ART-experienced subjects (35/44, 80%). Also clades A1 (n=1), C (n=2), F (n=2) and F1 (n=3) were represented in the ART-experienced group. One subject (# 67) recorded different clades (B and AG) at different visits, and a switch of samples is suspected. The ART-naïve subjects were infected only with non-clade B virus, with clade A virus making up the major group (8/16, 50%) followed by clade F and F1 (5/16, 31%), treated with FPV/RTV. Other clades included A1 (n=1), C (n=1) and G (n=1). The distribution of clades reflects the geographic origins of the different populations (e.g. ART-naïve subjects were recruited mainly from the Russian Federation and Romania).

Baseline plasma HIV-1 RNA levels and $CD4^+$ counts of enrolled subjects are shown in Table 12. Plasma HIV-1 RNA levels was quantified using the Roche Amolicor HIV-1 Monitor ™ Test (ultrasensitive; LLOQ] = 50 copies/mL). A total of 39% (29/74) of subjects had median plasma HIV-1 RNA values >100,000 copies/mL. Although a higher proportion of subjects (67%) in the FPV group had this level of HIV-1 RNA compared to the FPV/RTV group (30%), this was largely due to younger age and predominantly ART-naïve status.

The apparent $CD4^+$ cell count differences across the ages is difficult to interpret, given the different cut-off values for normal levels of $CD4^+$ cell counts in children under the age of six. Table 12 shows that children 2-5 years old in FPV treatment group had median $CD4^+$ cell count of 809 cells/mm^3 whereas those in the same age group in the FPV/RTV treatment group had $CD4^+$ cell count of 690 cells/mm^3.

Table 12: Plasma HIV-1 RNA levels and $CD4^+$ cell counts at baseline for APV29005 ITT(E) population by treatment and age group (Source NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 80, Table 17)

	FPV N=18	FPV/RTV N=57				
	2-5 Years N=18	2-5 Years N=3	6-11 Years N=25	12-18 Years N=29	FPV/RTV Total N=57	Total N=75
Baseline HIV-1 RNA, n	18	3	24	29	56	74
Median plasma HIV-1 RNA log_{10} copies/mL, (IQR)	5.1 (4.9, 5.6)	4.4 (4.2, 4.5)	4.5 (4.0, 5.1)	4.6 (4.1, 5.2)	4.5 (4.1, 5.1)	4.7 (4.1, 5.2)
HIV-1 RNA copies/mL, n (%)						
400–<5000	1 (6)	0	5 (21)	3 (10)	8 (14)	9 (12)
5000–<100,000	5 (28)	3 (100)	12 (50)	16 (55)	31 (55)	36 (49)
100,000–<250,000	6 (33)	0	6 (25)	7 (24)	13 (23)	19 (26)
250,000–<500,000	2 (11)	0	1 (4)	1 (3)	2 (4)	4 (5)
≥500,000	4 (22)	0	0	2 (7)	2 (4)	6 (8)
Baseline CD4+ cell counts (absolute), n	17	3	25	29	57	74
Median CD4+ cells/mm^3 (IQR)	809 (520, 941)	690 (543, 1337)	416 (288, 720)	247 (102, 419)	362 (180, 608)	418 (247, 720)
CD4+ cells/mm^3, n (%)						
<100	0	0	0	7 (24)	7 (12)	7 (9)
100-<200	0	0	4 (16)	6 (21)	10 (18)	10 (14)
200-<350	0	0	5 (20)	6 (21)	11 (19)	11 (15)
350-<500	4 (24)	0	6 (24)	4 (14)	10 (18)	14 (19)
≥500	13 (76)	3 (100)	10 (40)	6 (21)	19 (33)	32 (43)

XI (a) Previous antiretroviral therapy status of subjects enrolled in the study APV 29005

A summary of the ART and PI status for the ITT (E) Population by age at entry is presented in Table 13.

Table 13: Summary of ART status and PI status of subjects enrolled in the study APV29005 ITT(E) (Source NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 83, Table 19)

	FPV N=18	FPV/RTV N=57		
ART/PI status, n (%)	2-5 Years N=18	2-5 Years N=3	6-11 Years N=25	12-18 Years N=29
ART-naïve/PI-naïve	16 (89)	0	1 (4)	8 (28)
ART-experienced/PI-naïve	2 (11)	0	7 (28)	11 (38)
ART- and PI-experienced	0	3 (100)	17 (68)	10 (34)

Sixty-seven percent (50/75) of the subjects in the study were ART-experienced with 60% (30/50) of these subjects being PI-experienced. Interestingly, in the 12 to 18 year old age group, eight subjects (28%) were ART-naïve and 11 subjects (38%) were ART-experienced but PI-naïve. However, more subjects (17/25, 68%) in the 6 to 11 year old group were ART- and PI-experienced compared with the older age group (10/29, 34%).

XI (b) Prior PI antiretroviral therapy status of subjects enrolled in APV29005 study

In accordance with the inclusion criteria, all PI-experienced subjects were previously treated with ≤3 PIs excluding agenerase and fosamprenavir. Most of the PI-experienced subjects (n=30) had one prior PI exposure (67%), with NFV being the most commonly prescribed PI. The median duration of prior PI exposure was 253 weeks. The number of subjects with prior PI antiretroviral therapy is summarized in Table 14.

Table 14: summary of prior PI antiretroviral therapy in the PI-experienced population in APV29005 ITT (E) population (Source NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 84, Table 20)

	FPV/RTV PI-experienced N=30
No. (%) of PI taken	
No. (%) of subjects	30 (100)
1	20 (67)
2	9 (30)
3	1 (3)
PIs taken	
No. (%) of subjects	30 (00)
ATV + RTV	1 (3)
IDV	2 (7)
LPV/RTV	3 (10)
NFV	25 (83)
RTV	9 (30)
SQV + RTV	1 (3)
Median duration of all prior PI exposure (Weeks)	
Median (range)	253 (27-423)

XII. Effect of FPV and FPV/RTV BID treatment on virologic response

The median HIV-1 RNA levels by PI status and visit for the ITT (E) population are shown in Table 15.

Table 15: Median plasma HIV-1 RNA by visit and PI status in APV29005 ITT (E) population (Source NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 92, Table 27)

	Plasma HIV-1 RNA (log_{10} copies/mL) Median [IQR]							
	FPV		FPV/RTV					
Week	PI-naïve N=18	n	PI-naïve N=27	n	PI-exp N=30	n	FPV/RTV Total N=57	n
Baseline	5.13 [4.90, 5.62]	18	4.60 [4.11, 5.22]	27	4.46 [4.06, 4.85]	29	4.53 [4.07, 5.10]	56
Week 2	3.39 [3.05, 3.97]	12	3.11 [2.72, 3.42]	18	2.89 [2.57, 3.26]	23	2.94 [2.60, 3.35]	41
Week 4	3.18 [2.70, 3.60]	16	2.54 [2.26, 2.89]	20	2.67 [1.82, 3.07]	23	2.60 [2.04, 2.91]	43
Week 8	2.59 [1.69, 2.86]	17	2.26 [1.78, 2.84]	24	2.54 [1.69, 3.38]	26	2.38 [1.75, 2.84]	50
Week 12	2.07 [1.77, 2.60]	16	1.74 [1.69, 2.23]	24	2.25 [1.69, 3.73]	24	2.08 [1.69, 2.72]	48
Week 16	1.92 [1.69, 2.57]	15	1.69 [1.69, 1.83]	21	2.04 [1.69, 3.83]	20	1.71 [1.69, 2.49]	41
Week 24	2.22 [1.69, 2.60]	13	1.69 [1.69, 2.04]	21	1.80 [1.69, 3.20]	25	1.69 [1.69, 2.59]	46

Table 15 shows that by Week 16, the majority of PI-naïve subjects in the FPV/RTV group had reached LLOQ (50 copies/mL) and remained undetectable at Week 24. Though the majority of the PI-naïve subjects in the FPV group failed to achieve the LLOQ, they had a higher median plasma HIV-1 RNA value at baseline than those in the FPV/RTV group. For the PI-experienced cohort treated with FPV/RTV, median HIV-1 RNA decreased continuously through Week 24 to a median of 1.80 log_{10} copies/mL.

XIII. Summary of study outcome at week 24 using the TLOVR analysis for ITT (E) population (study APV29005)

A summary of the study outcomes at Week 24 using the TLOVR analysis in the ITT (E) population by PI status is summarized in Table 16.

Table 16: Summary of study outcomes (<400 copies/mL) at Week 24 by PI Status in APV29005 ITT(E) Population (TLOVR) [Source NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 95, Table 30]

Outcome	FPV PI-naïve N=18 n (%)	FPV/RTV PI-naïve N=27 n (%)	FPV/RTV PI-exp N=30 n (%)	Total N=75 n (%)
Responders (<400copies/mL plasma HIV-1 RNA)	12 (67)	19 (70)	17 (57)	48 (64)
Primary reason for failure (non-responders)				
Virologic failure	2 (11)	3 (11)	9 (30)	14 (19)
Plasma HIV-1 RNA rebound	0	1 (4)	0	1 (1)
Never achieved viral load suppression by Week 24	2 (11)	2 (7)	9 (30)	13 (17)
Discontinued study drug before achieving suppression	2 (11)	3 (11)	4 (13)	9 (12)
Due to an adverse event	0	1 (4)	1 (3)	2 (3)
Due to consent withdrawn	0	1 (4)	1 (3)	2 (3)
Not discontinued but no data at Week 24 and beyond	1 (6)	0	1 (3)	2 (3)
Due to other reason	1 (6)	1 (4)	1 (3)	3 (4)
Discontinued study drug while suppressed	2 (11)	2 (7)	0	4 (5)
Not discontinued but no data at Week 24 and beyond	2 (11)	2 (7)	0	4 (5)

Table 16 shows that 14 subjects were virologic failure (plasma HIV-1 rebound, or never suppressed). Of the 14 subjects with virologic failure, six were receiving FPV tablets, and eight were receiving FPV oral suspension.

Of those 13 subjects who never achieved VL suppression (<400 copies/mL) by Week 24, two eventually withdrew from the study; subject # 42 who was PI-naïve and receiving FPV withdrew from the study due to insufficient viral load response and subject # 306 who was PI-experienced and receiving FPV/RTV withdrew due to compliance issues.

One subject experienced viral rebound by Week 24: subject # 19, a 15-year-old PI-naïve subject in the FPV/RTV group, had a baseline VL of 35,800 copies/mL which was suppressed to <50 copies/mL at Week 12 but rebounded by Week 24 to 26,400 copies/mL. This subject's plasma HIV-1 RNA was re-suppressed at Week 36 (2,360 copies/mL) but increased again at Week 48 (9,830 copies/mL).

Two subjects (both in the FPV/RTV group) had discontinued study drugs by Week 24 due to an AE.

Discontinuation of study drug before achieving suppression due to "Other" reasons included non-compliance (n=1), subject does not take study medication (n=1) and subject refused liquid (n=1). All three subjects were receiving FPV oral suspension.

Six subjects did not have the opportunity to reach Week 24 by the data cut-off date of 22 May 2006 and were therefore regarded as non-responders at Week 24 in the TLOVR analysis. The reason for failure was documented in Table 16 as 'not discontinued but no data at Week 24 and beyond'.

XIV. Genotypes of baseline matched on-therapy isolates from virologic failure subjects in study APV20095

Genotypes of baseline isolates were determined from 57 subjects using Genseq methods. Genotypes of baseline matched on-therapy HIV-1 isolates were determined from 14 virologic failure subjects (HIV-1 RNA >400 copies/mL) at Week 24 and/or Week 48. Additionally genotypes of on-therapy isolates were determined from 8 subjects at Weeks 4, or Week 60 by investigators.

Virologic failure subjects (ART-naïve subject treated with FPV (subject # 52) and two ART-experienced, PI-naïve subjects (subjects # 19 and 91) treated with FPV/RTV were infected with non-clade B virus. Other virologic failure subjects (n=11) were infected with clade B virus (NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 153).

Of the 14 subjects with virologic failure at Week 24 (≥400 copies/mL, ITT [E] TLOVR) genotypes of on-therapy isolates were available from 9 subjects, data for five subjects (#s 42, 52, 66, 81, and 306) were not available. Genotypes of on-therapy isolates from two PI-experienced subjects with virologic failure (subjects # 231 and 317) were available but matched baseline genotypes were missing. In addition to 14 virologic failure subjects, genotypes of on-therapy isolates from 8 other subjects (1, 12, 59, 67, 79, 93, 191, and 201) were determined at the request of investigators for clinical management. Of these, matched baseline genotypes were available for isolates from 7 subjects. Genotypic analysis for baseline isolate from one subject (# 210) was unsuccessful.

The genotypes of baseline matched on-therapy isolates are shown in Table 17.

Table 17: Genotypes of baseline and on-therapy isolates from ART-experienced, PI-naïve subjects with virologic failure (Source: (NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 162, Table 80).

Subject ID	Visit	Plasma HIV-1 RNA (copies/mL)	PI-mutations*
19	Day 1	35,8000	[redacted]
	Week 24	26,400	
91	Day 1	140,000	
	Week 24	7900	
182	Day 1	9000	
	Week 24	33000	

*= newly emerged mutations

b(4)

Table 17 shows that on-therapy isolates from subject # 91 developed APV resistance-associated mutation I50V, I54M, and I84V during therapy. These subjects received FPV/RTV treatment. Subject 91 was 6-11 years and subjects 19 and 182 were 12-18 years old. Subject # 19 initially responded to therapy, but plasma HIV-1 RNA rebounded at Week 24. Subjects 91 and 182 did not achieve viral RNA suppression and amino acid changes in protease of Week 24 isolates from baseline were not observed.

Table 18: Genotypes of baseline and on-therapy isolates from PI-experienced subjects with virologic failure (Source: NDA 22-116, GSK study report RM2006/00532/00, APV 29005, Page 164, Table 81).

Subject ID	Visit	Plasma HIV-1 RNA (copies/mL)	PI-mutations
101	Day1	120,000	[redacted]
	Week 24	24,000	
102	Day 1	29,000	
	Week 24	11,000	
131	Screen	15, 000	
	Day 1	1100	
	Week 24	1600	
	Week 84	ND	
142	Screen	5100	
	Day 1	1700	
	Week 24	3300	
231	Day 1	14000	
	Week 24	31000	
317	Day 1	382,000	
	Week 24	19,000	

b(4)

ND= not done, NR= attempted, no result
Subject No. 101, 131 and 317 were 6 to 11 years, other subjects were 12-18 years old.
All subjects received FTV/RTV.

Table 18 shows that on-therapy isolates from subjects 101 and 131 developed APV resistance associated mutations, I50V, I54M, V82F/I (subject # 101) and I84V (subject # 131). Genotypes of isolates at baseline were not available from subject # 231 and #317, However, on-therapy isolates from these two subjects selected for APV-resistance associated mutations I54L/V during therapy. In addition other major PI mutations e.g., L33F, M46I and V82A, L90M were also present in on-therapy isolates from these 2 subjects. On-therapy isolates from subjects # 102 and 142 contained mutations K20I, D30N, M36I, M46I, and L90M were present in on-therapy isolates.

XV. Genotypes of baseline and on-therapy isolates from subjects selected by the Investigators

Genotypes of baseline and on-therapy isolates were available from 6 of 8 subjects (# 1, 12, 59, 79, 93, and 191) selected by the investigators for clinical management (NDA 22-116. GSK study report RM2006/00532/00, APV 29005, Page 167, Table 82). Of these, subject # 12, and 93 were virologic failure at Week 24 (HIV-1 RNA $\geq$400 copies/mL) at Week 24. Genotypes of on-therapy isolates from subject # 1, 59, and 79 were available only for Week 4. There was no change from baseline at Week 4 in genotype of on-therapy isolates from subject # 1, 59, 79. Similarly, no new protease resistance mutations were detected in on-therapy isolates from subject # 12 and 93 at Week 24 and Week 60, respectively. On-therapy isolates from subject # 191 developed APV resistance-associated mutations I54V in combination with K20R, M36I, L63P andV82A at Week12 and this mutation was maintained in isolates at Week 60. Subject # 191 had plasma HIV-1 RNA levels of 140 and 62 copies/mL at Weeks 12 and 60, respectively. Genotypes of baseline isolates from subject # 201 were not available. On-therapy isolates from this subject at Week 4 contained APV resistance associated mutation I54V in combination with mutations L10V, K20R, D30N, M36I, A71T, N88D and L90M (NDA 22-116. GSK study report RM2006/00532/00, APV 29005, Page 167, Table 82). Genotypes of on-therapy isolates from subject # 67 were not available.

XV. Phenotypes of baseline and on-therapy isolates from subjects with treatment emergent APV resistance-associated mutations

Drug susceptibilities of treatment emergent baseline matched on-therapy isolates are shown in Table 19.

Table 19: Phenotypes of baseline matched on-therapy isolates with treatment emergent APV resistance associated mutations (Source: NDA 22-116, study APV29005, Study report RM2206/00532/00, Page 170, Table 84)

Subject*	Isolates at	APV (Fold changes)
91	Day 1	1.69
	Week 24	14
101	Day 1	3.31

	Week 24	16
	Week 36	53
131	Screening	7.64
	Week 24	8.7
	Week 84	42

- **= virologic failure**

As shown in Table 19, on-therapy isolates from 3 subjects (# 91, 101, 131) exhibited 8.67 to 42 fold resistance to APV. However, baseline isolates from subject # 101 and 131 were also resistant to APV. On-therapy isolates from subject # 231 and 317 also exhibited 42- and 7.12-fold decrease in susceptibility to APV, respectively. However, data on the phenotypes of baseline isolates from subject # 231 and 317 were not available (NDA 22-116, study APV29005, Study report RM2206/00532/00, Page 170, Table 84).

Isolates from subject 101 exhibited 3.3- and 16-fold resistance to APV at baseline and Week 24. The high level resistance at Week 24 coincided with the emergence of APV resistance-associated mutations I50V, and I54M in combination with V82F/I mutations. Similarly, decreases in APV susceptibility for on-therapy isolates for subject # 91 (1.69- to 14-fold) was also associated with the selection of APV resistance-associated mutations L33F, I50V, I54M, and I84V. Isolates from subject #131 exhibited 7.64-fold-reduced susceptibility to APV at baseline and 8.0-fold change in resistance at Week 24 However, with the emergence of I84V mutation at week 84, the fold resistance of Week 84 isolates to APV increased by 5.5 fold (to 42). Thus phenotypes of on-therapy isolates correlated with the genotypic changes.

XVI. Cross-resistance of on-therapy isolates to PIs (IDV, LPV, NFV, RTV, SQV

A summary of PI cross-resistance for isolates showing APV resistance together with genotypes are shown in Table 20. On-therapy and baseline isolates (where available) from 3 subjects with APV resistance associated mutations were tested for susceptibility to ATV, IDV, LPV, NFV, RTV, RTV, SQV and TPV. Table 20 shows that baseline isolates from subject #101 and131 were cross-resistant to most PIs tested (ATV, IDV, LPV, NFV, RTV, and SQV). However, baseline isolates were susceptible to TPV depending on the number of mutations, combination and mutations in the PR gene. On-therapy isolates from subject # 91, 101 and 131 were cross-resistant to most of the PIs tested except for TPV (where tested). On-therapy isolates from subject 91 and 131 exhibited 0.76- to 8.1-fold change in EC_{50} values of TPV compared to wild-type HIV-1 isolates.

Table 20: Cross-resistance of APV resistant baseline and on-therapy isolates to approved PIs (Source: NDA 22-116, GSK study report RM2206/00532/00, Pages 172-173, Table 85)

Subject	Visit	APV mutation	Phenotype							
			FPV/r	ATV/r	IDV/r	LPV/r	NFV	RTV	SQV	TPV

ID										
91	Week 24	[redacted]	14	3.73	8.24	68	20	90	8.87	0.76
101	Baseline		3.31	12	16	6.09	112	12	17	1.85
101	Week 36		53	6.96	30	95	23	>169	5.92	ND
131	Baseline		7.64	54	25	98	82	>242	54	2.32
131	Week 84		42	61	9.33	41	34	>297	70	8.01

b(4)

Study APV 20002

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

OBJECTIVES

Primary

1. To define the FPV twice daily (BID) dosage regimen(s) which will provide target steady state plasma APV exposure to HIV-1 infected PI-naïve pediatric subjects aged 4 weeks to <6 months.
2. To define the FPV/RTV BID dosage regimen(s) which will provide target steady state plasma APV exposure to HIV-1 infected pediatric subjects aged 4 weeks to <2 years.
3. To evaluate the safety and tolerability of FPV in HIV-1 infected pediatric subjects aged 4 weeks to <6 months and FPV/RTV in subjects 4 weeks to <2 years when administered as a component of combination therapy.

Secondary

1. To evaluate the antiviral activity of FPV in HIV-1 infected pediatric subjects aged 4 weeks to <6 months and FPV/RTV in subjects 4 weeks to <2 years, in combination with nucleoside reverse transcriptase inhibitor (NRTI) therapy.
2. To evaluate the immunologic activity of FPV in HIV-1 infected pediatric subjects aged 4 weeks to <6 months and FPV/RTV in subjects 4 weeks to <2 years in combination with NRTI therapy.
3. To assess systemic exposure to FPV when administered to HIV-1 infected pediatric subjects aged 4 weeks to <2 years.

4. To assess plasma RTV area under the concentration-time curve over the dosing interval on multiple dosing (AUC[0-τ]), maximum plasma concentration (C_{max}), and concentration at the end of a dosing interval at steady state (Cτ) following multiple dose administration of FPV/RTV BID.
5. To investigate the relationship of steady state plasma APV PK parameters to changes in plasma HIV-1 ribonucleic acid (RNA) concentrations, helper-inducer T-lymphocyte surface antigen ($CD4^+$) percentages and/or the occurrence of AEs.
6. To assess subject adherence, the shaking of the FPV oral suspension prior to administration and parent/guardian perceptions of study medications.
7. To assess viral resistance patterns and to compare these patterns with treatment outcome (where permissible by blood volumes).

APV20002 is an international, 48-week, Phase II, open-label, 2–cohort, multicenter study conducted in HIV-1 infected pediatric subjects 4 weeks to <2 years old.

Subjects in this study were enrolled into one of two cohorts to determine the FPV and FPV/RTV dosage regimens for pediatric subjects at various stages of physiologic development. Cohort 1 Arm A (6 to <24 months, FPV/RTV BID) was opened in parallel with Cohort 2 Arm A (4 weeks to <6 months, FPV/RTV BID). As per protocol amendment 3, Cohort 2 Arm B (4 weeks to <6 months, FPV BID) opened to recruitment in parallel to Arm A. No subjects have enrolled in Arm B (FPV BID) to date; therefore, this report is based on an interim analysis of subjects enrolled in Cohort 1 Arm A and Cohort 2 Arm A.

Microbiologic Specific Inclusion Criteria

A subject was eligible for inclusion in this study only if all of the following criteria applied:

1. Screening plasma HIV-1 RNA level ≥400 copies/mL.
2. Subjects who, in the investigator's opinion, and following viral resistance testing, were able to construct an active NRTI backbone regimen consisting of two NRTIs.
3 Subjects must meet one of the following criteria:

- Therapy naïve or PI-naïve subjects (defined as having received less than one week of any PI).
- PI-experienced subjects defined as having prior experience with no more than three PIs excluding APV. Prior RTV boosted PI therapy was considered as only one PI as long as the RTV dose was lower than that recommended for use of RTV as an antiretroviral agent.

Microbiologic Specific Exclusion Criteria

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. Prior history of having received APV.
2. NNRTI therapy within 14 days prior to study drug administration (single or multiple-dose) or anticipated need for concurrent NNRTI therapy during the study period.
3. PI therapy within 5 days prior to study drug administration (single or multiple-dose)
4. Treatment with radiation therapy or cytotoxic chemotherapeutic agents within 28 days of study drug administration or an anticipated need for such treatment within the study period.
5. Treatment with immunomodulating agents (e.g., systemic corticosteroids, interleukins, interferons) or any agent with known anti-HIV activity (e.g., hydroxyurea or foscarnet) within 28 days of study drug administration.
6. Treatment with other investigational drugs/therapies within 28 days prior to receiving study medication (note: treatments available through a Treatment investigational new drug (IND) or other expanded-access mechanism will be evaluated on a case-by-case basis in consultation with the sponsor).

Drug Dosing

FPV

No FPV without RTV (unboosted) BID dosing had occurred at time of this interim analysis.

FPV/RTV Dosing

For Cohort 1 (6 to <24 months) Arm A, steady-state PK data from the first 8 subjects allowed for the selection of a revised FPV/RTV 45/7 mg/kg BID regimen, and newly enrolled subjects initiated chronic dosing with this regimen.

For Cohort 2 (1 to <6 months) Arm A, an insufficient amount of steady-state PK data are currently available to allow selection of a FPV/RTV BID dosage regimen for the age group, so subjects continue to complete the single dose visit (SDVs) and receive individualized FPV/RTV BID dosage regimens.

Virology Population

All subjects with HIV-1 resistance testing data were included in this population.

There were 13 subjects enrolled at the time of this interim analysis, four of whom (# 7145, 7156, 7176, and 8488) withdrew from the study [NDA 221-116, GSK study report RM2006/00360/00 study APV 20002, Page 51, Table 7]. Subject # 7156 died of abdominal disorder that was considered unrelated to the investigational products by the investigators. Subject # 7176 had very low plasma concentrations of APV after receiving single doses of FPV and FPV/RTV at the SVDs and was withdrawn at the request of GSK. Subject #7145 discontinued at Week 16 due to lack of availability of RTV solution. Subject # 7155 withdrew during SDV1 due to difficulties with the PK

sampling. Subject # 8488 discontinued at Week 2 due to subject's decision to withdraw. Subject # 7162 had discontinued from the study due to virologic failure 1 day after the Week 84 visit with a follow-up visit 6 weeks later.

XVII. Baseline characteristics of subjects enrolled in study APV20002

The majority of subjects (7/10) had baseline plasma HIV-1 RNA levels greater than 250,000 copies/mL, with a median plasma HIV-1 RNA level of 5.6 $\log_{10}$ copies/mL. Five subjects had baseline $CD4^+$ cell counts ranging from 500-999 cells/mm^3 and five had CD4+ cell count ≥1,000 cells/mm3 (NDA 221-116, GSK study report RM2006/00360/00 study APV 20002, Page 54, Table 10).

XVIII. Prior antiretroviral therapy status of subjects enrolled in study APV20002

Of the 13 subjects in the safety population, five subjects (# 7155, 7156, 7160, 7161 and 7165) had received ART prior to entering the study. All five had received NFV co-administered with two NRTIs.

XIX. Efficacy of FPV/RTV BID on virologic response

The median plasma HIV-1 RNA level generally decreased with time. By Week 36, the median plasma HIV-1 RNA level had reduced from 5.59 $\log_{10}$ copies/mL at baseline to below the lower limit of quantification of the assay (50 copies/mL or 1.69 $\log_{10}$ copies/mL).

Table 21: Median plasma HIV-1 RNA ($\log_{10}$ copies/mL) by visit and change from baseline ITT (E) population (NDA 221-116, GSK study report RM2006/00360/00, Page 58, Table 14).

	FPV/RTV BID N=10		
Week	Median (IQR)	Change from Baseline Median (IQR)	n
Baseline	5.59 (5.20, 6.04)		10
Week 4	3.11 (2.88, 3.23)	-2.34 (-2.54, -2.01)	9
Week 12	2.05 (1.93, 2.71)	-3.37 (-3.47, -2.51)	9
Week 24	1.93 (1.69, 2.11)	-3.70 (-4.33, -2.83)	7
Week 36	1.69 (1.69, 1.74)	-3.80 (-4.19, -2.62)	8
Week 48	1.69 (1.69, 1.74)	-3.80 (-4.24, -3.51)	8

XX. Genotypes and phenotypes of baseline and on-therapy isolates from subjects enrolled in study APV20002

Virology population for HIV-1 resistance testing consisted of 8 subjects; 5/8 were ART-naïve at study entry and 3/8 had been previously treated with NFV and two NRTIs. Genotypes of baseline isolates were available from 7 subjects who achieved plasma HIV-1 RNA levels <400 copies/mL at Week 48. Six of these subjects achieved plasma HIV-1 RNA levels <50 copies/mL. Genotypes of on-therapy isolates were available from one virologic failure subject (# 7162). However, phenotypes of baseline isolates from this subject were not available. Genotypic analysis of baseline isolates from 7 subjects showed that none (0/7) had any major mutations associated with resistance to PIs (NDA 221-116, GSK study report RM2006/00360/00 study APV 20002, Page 76., Table 27). Accessory mutations L10I, K20R, M36I, L63P, A71T, and V77I were present in different combinations (1-5) in baseline isolates from 5/7 subjects. Baseline isolates from 2 subjects (# 7161, and 7163) did not contain any accessory mutations associated with PI resistance.

On-therapy isolates from subject # 7162 developed APV resistance-associated mutations [ ] at Week 84. HIV-1 RNA for this subject at baseline was 1,100,000 and >75,000 copies/mL at Week 84 (NDA 22-116, GSK study report RM2006/00360/00, Page 76. Table 27). b(4)

Phenotypic analysis showed that baseline isolates from all subjects were susceptible to APV, ATV, IDV, LPV, NFV, RTV and SQV (NDA 22-116, GSK study report RM2006/00360/00, Page 77, Table 28). On-therapy isolates from subject # 7162 at week 84 showed 14-fold resistance to APV, and cross resistance to NFV, RTV, and SQV. However, on-therapy isolates from subject # 7162 at Week 84 were susceptible to ATV/r, IDV/r and LPV/r (NDA 22-116, GSK study report RM2006/00360/00, Page 77, Table 28).

CONCLUSIONS

APV 20003 was an international , 48 week , Phase II, open-label, multi-cohort, multicenter study conducted in 69 HIV-1 infected subjects 2 to < 18years old. The median plasma HIV-1 RNA at baseline for subjects 2 to 5 years, 6 to 11 years and 12 to 18 years were 4.8, 4.8 and 4.9 $\log_{10}$ copies/mL, respectively. Thirty-seven of 69 subjects enrolled in study APV20003 had received prior PI-treatment. A majority of subjects had received NFV followed by RTV or IDV. At weeks 48, the median HIV-1 RNA decrease from baseline was 2.65 $\log_{10}$ copies/mL in prior PI-naïve (n=21) and 1.65 $\log_{10}$ copies/mL in prior PI-experienced (n=25) subjects enrolled in the study APV20003. Genotypes of baseline matched on-therapy isolates were available from 16 virologic failure subjects on FTV/RTV QD treatment in study APV20003. Of these, on-therapy isolates from 5 subjects developed APV-resistance-associated mutations during therapy. Substitutions associated with resistance to other proteases present in baseline isolates were maintained in on-therapy isolates from 9 subjects. However, no new mutation developed during therapy in on-therapy isolates from these subjects. Similarly, both baseline and on-therapy isolates from 2 prior PI-naïve subjects did not contain any substitutions associated with resistance to APV. Additionally, on-therapy isolates from 3

of 12 subjects clinically managed by the investigators developed APV-resistance associated substitutions.

Phenotypic analysis showed that baseline isolates from 3 subjects (# 6492, 6994, 7012) exhibited 3.0- to 3.5- fold resistance to APV. Baseline isolates from these subjects contained primary protease resistance-associated substitutions V82A/T, I84V, and L90M. On-therapy isolates from these subjects exhibited 4.43- to 38-fold resistance to APV. Additionally, on therapy isolates from two other subjects (# 7059 and 7256) exhibited 4.03- and 4.91-fold resistance to APV. On-therapy isolates from one of these subjects (# 7256) developed APV resistance-associated substitutions L33F and I54L and another subject (3 7059) contained substitutions L10F, D30N, M36I, L63P V77I and N88D. On-therapy isolates from one additional subject (# 6353) developed substitutions L33F, A71T and L90M during therapy and exhibited 4.19- and 5.19-fold resistance at weeks 24 and 36,

For the investigator requested subjects, samples for baseline phenotypic analysis were not available for comparison except for one subject. On therapy isolates from 4 subjects exhibited 2.24- to 12.0-fold resistance to APV at Week 48. Isolates from 3 of these 4 subjects developed APV-resistance-associated substitutions I47V, I54L/M, I84V during therapy. On-therapy isolates from another subject exhibited 2.24-fold resistance to APV and both baseline and on-therapy isolates from this subject contained APV resistance-associated substitution I54V in combination with substitutions L10I, L63P, A71T and V82A. The phenotypes of baseline and on-therapy isolates correlated with genotypes. Most APV resistant isolates were cross-resistant to IDV, RTV, SQV and susceptible to LPV.

In study APV20095, subjects received FPV BID or FPV/RTV BID. In study 29005, subjects were infected with different HIV-1 clades. However, clade B was most prevalent in ART experienced subjects; 80% (35/44). A majority (50%, 8/16) of ART-naïve subjects were infected with clade A virus followed by clade F and F1 (5/16). Other clades included A1 (n=1), C (n=1) and G (n=1). Sixty-seven percent (50/75) of the subjects in the study APV 0095 were ART experienced with 60% (30/50) of these subjects being PI-experienced. Fourteen subjects were virologic failure. Of the 14 virologic failure subjects, genotypes of on-therapy isolates were available from 9 subjects. On-therapy isolates from one subject (#91) from the prior PI-naïve treatment group developed APV resistance-associated substitutions I50V, I50V, I54M and I84V during therapy. Among subjects with prior PI-experience, isolates from two subjects developed APV resistance associated substitutions (I50V, I54M.V82F/I and I84V.

Genotypes of baseline and on-therapy isolates were available from 8 subjects selected by the investigators for clinical management. Of these two subjects were virologic failures at Week 24. No new mutations associated with resistance to proteases were detected in on-therapy isolates of these 2 virologic failure subjects.

Phenotypic analysis showed that on-therapy isolates from 3 virologic failure subjects exhibited 8.67- to 42-fold resistance to APV. However, baseline isolates from 2 of these subjects were also resistant to APV. The phenotypes of on-therapy and baseline isolates correlated with the genotypes.

In study APV 20002, genotypes of on-therapy isolates were available from one virologic failure subject. However, phenotypes of baseline isolates from this subject were not available. On-therapy isolates from this virologic failure subject developed APV resistance-associated substitutions L33F, I54L and I84V at Week 84. HIV-1 RNA for this subject at baseline was 1,100,000 and >75,000 copies/mL at Week 84.

Phenotypic analysis showed that on-therapy isolates from this subject exhibited at week 14-fold resistance to APV at Week 84 and cross resistance to NFV, RTV, and SQV. However, on-therapy isolates from this subject at Week 84 were susceptible to ATV/r, IDV/r and LPV/r.

MICROBIOLOGY LABEL (06/12/07)

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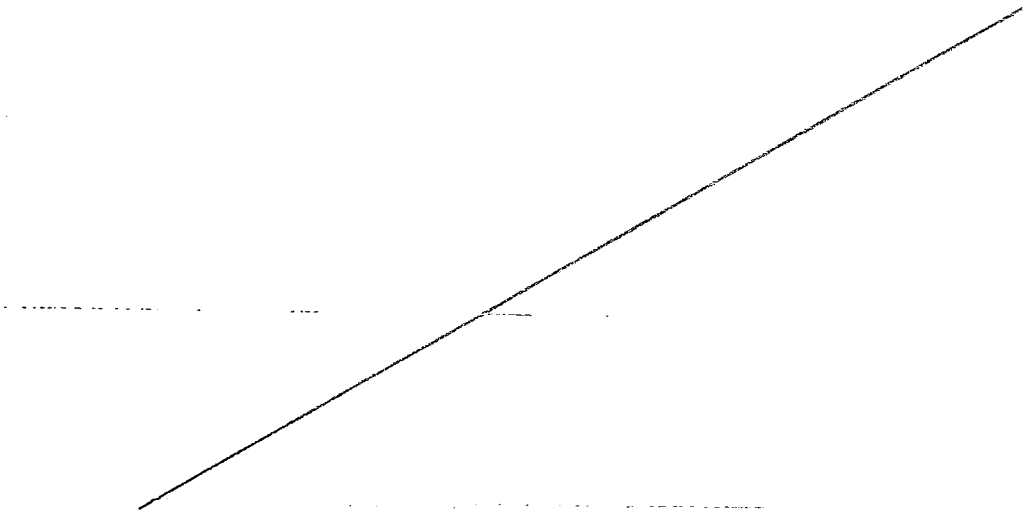

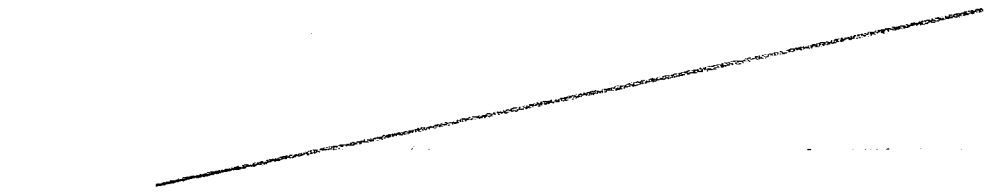

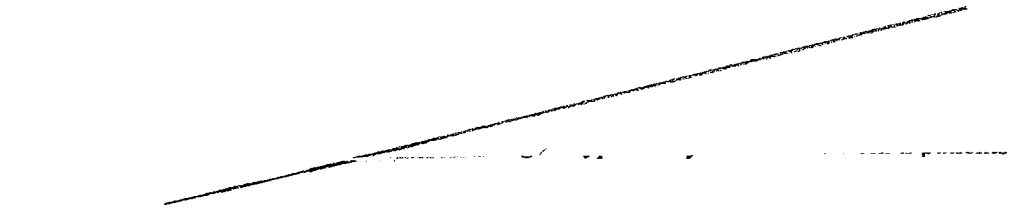

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RECOMMENDATIONS

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
NDA 22-116; SN 000, Review Completed 05/29/07

With respect to microbiology, NDA 22-116 is approvable.

Lalji Mishra, Ph.D.
Microbiologist

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