APV10012

TITLE: A Phase I, Open, Randomized, Balanced, Incomplete Crossover Drug-Drug Interaction Study to Assess the Steady-State Plasma Amprenavir and Lopinavir Pharmacokinetics following Administration of Lopinavir 400mg/Ritonavir 100mg BID + GW433908 700mg BID + Ritonavir 100mg BID, GW433908 700mg BID + Ritonavir 100mg BID, or Lopinavir 400mg/Ritonavir100mg BID for 14 days in Healthy Adult Subjects.

BACKGROUND: From AGENERASE + LPV/RTV data generated by Abbott Laboratories and from AGENERASE + RTV data generated by GSK, it appears that LPV 400mg/RTV 100mg BID increases plasma APV concentrations significantly less than RTV 100mg BID alone. In addition, KALETRA product labeling states that APV decreased plasma LPV AUC values by ~15% when the drugs were co-administered for 5 days. This study evaluated whether the addition of RTV to the combination of GW433908 + LPV/RTV delivers similar plasma APV and LPV exposure as those observed with each standard regimen of GW433908 + RTV and LPV/RTV alone. These data were intended to facilitate GW433908 and RTV dose selection when dosed with KALETRA for potential Phase III study in PI experienced patients.

OBJECTIVES: The primary objectives were to compare plasma amprenavir (APV) pharmacokinetics following administration of GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID for 14 days versus GW433908 700mg BID + RTV 100mg BID for 14 days and to compare plasma Lopinavir (LPV) PK following administration of GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID for 14 days versus LPV 400mg/RTV 100mg BID for 14 days. The secondary objective was to assess the safety and tolerability of co-administering GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID in healthy adult subjects.

SUBJECTS AND STUDY DESIGN: This was a Phase I, open, randomized, balanced, 4-arm, 2-period, multiple-dose, incomplete crossover study conducted in 36 healthy adult subjects at one study center in the US. Thirty-six subjects were randomized to one of the following arms:

Arm	Sample Size	Period 1 (Days 1-15)	28 Day Washout	Period 2 (Days 1-15)
A	9	Treatment 1		Treatment 3
B	9	Treatment 3		Treatment 1
C	9	Treatment 2		Treatment 3
D	9	Treatment 3		Treatment 2

Treatment 1 = GW433908 700mg BID + RTV 100mg BID for 14 days
Treatment 2 = LPV 400mg/RTV 100mg BID for 14 days
Treatment 3 = GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID (total of 200mg RTV BID) for 14 days

Subjects were instructed to take the study drugs with food in the morning and in the evening, with approximately 12 hours between doses. In both periods, subjects returned to the study center the evening of Day 13 in preparation for the Day 14 assessments. One APV and/or LPV PK sample was collected the evening of Day 13, immediately prior to receiving the evening dose of study drugs. Subjects fasted overnight for at least 10 hours (water allowed ad libitum). On the morning of Day 14, subjects were served a standard moderate fat meal which was to be ingested within 30 minutes. Within 15 minutes after completion of the meal, a pre-dose blood sample was taken, immediately followed by administration of the last dose of Period 1 or 2 study drug. The dose was administered with 180mL (6oz) of water. Additional water was allowed ad libitum starting 2 hours post-dose. Following administration of the last dose of Period 1 or 2 study drug on Day 14, subjects underwent 12-hour plasma PK sampling. Subjects stayed overnight at the study center and on the morning of Day 15 provided an additional plasma PK sample 24 hours post-dose.

Thirty-six subjects were enrolled and twenty of these 36 subjects completed the study (10 in Arms A and B and 10 in Arms C and D). The overall demographic characteristics of these were as following: Male (70%) and female (30%); White (75%), Blacks, Asians and Hispanics (25% combined).

INVESTIGATOR AND STUDY LOCATION:

FORMULATION: GW433908 700mg tablet (E01B93), Norvir (ritonavir) 100mg capsule, Kaletra (LPV/RTV) 133.3mg/33.3mg capsules.

SAMPLE COLLECTION: Blood samples for measurement of plasma APV and LPV concentrations were collected over 12 hours at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post morning dose on Day 14, and 24 hours post Day 14 dose on Day 15.

ASSAY: Plasma samples were analyzed for APV and LPV by GSK Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics, Research Triangle Park, NC, USA, using a validated method. The quality control samples had coefficients of variation less than or equal to respectively for APV and lopinavir.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for AUC_{τ}, Cmax and C_{τ} were provided for each group.

PHARMACOKINETIC RESULTS:

Table 1. Steady-State Plasma APV PK Parameter Estimates, Geometric Mean (95% CI)

Plasma APV PK Parameter	Treatment 1 Arms A & B (N=10)	Treatment 3 Arms A & B (N=10)
$AUC_{\tau,ss}$ (µg.h/mL)	31.2 (24.6-39.6)	11.3 (8.1-15.7)
$C_{max,ss}$ (µg/mL)	4.61 (3.57-5.96)	1.88 (1.24-2.84)
$C_{\tau,ss}$ (µg/mL)	2.10 (1.64-2.67)	0.72 (0.52-1.00)
$t_{max,ss}$ (h)[a]	3.00 (0.75-5.00)	3.50 (1.50-5.00)

a $t_{max,ss}$ data presented as median (range)
Treatment 1 = GW433908 700mg BID + RTV 100mg BID for 14 days
Treatment 3 = GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID (total of 200mg RTV BID) for 14 days

Table 2. Steady-State Plasma APV PK Treatment Comparisons, GLS Mean Ratio (90% CI)

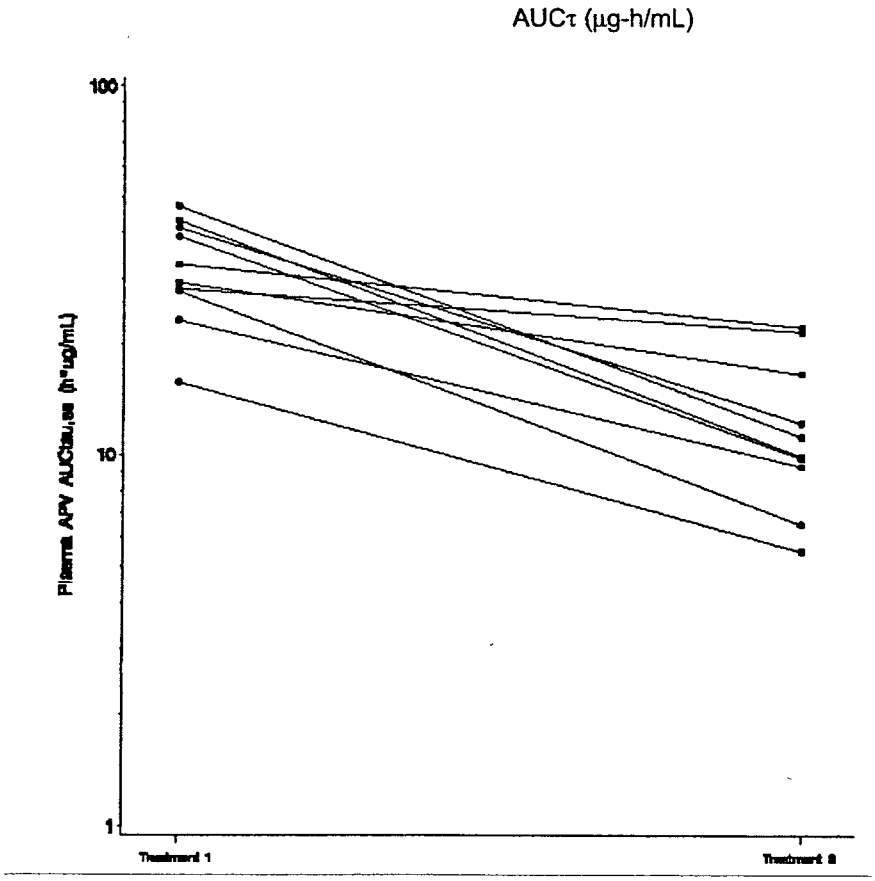
Plasma APV PK Parameter	Treatment 3/Treatment 1 Arms A & B (N=10)
$AUC_{\tau,ss}$ (µg.h/mL)	0.37 (0.28-0.49)
$C_{max,ss}$ (µg/mL)	0.42 (0.30-0.58)
$C_{\tau,ss}$ (µg/mL)	0.35 (0.27-0.46)
$t_{max,ss}$ (h)[a]	1.06 (0.71-1.40)

a LS mean ratio (90% CI) for $t_{max,ss}$

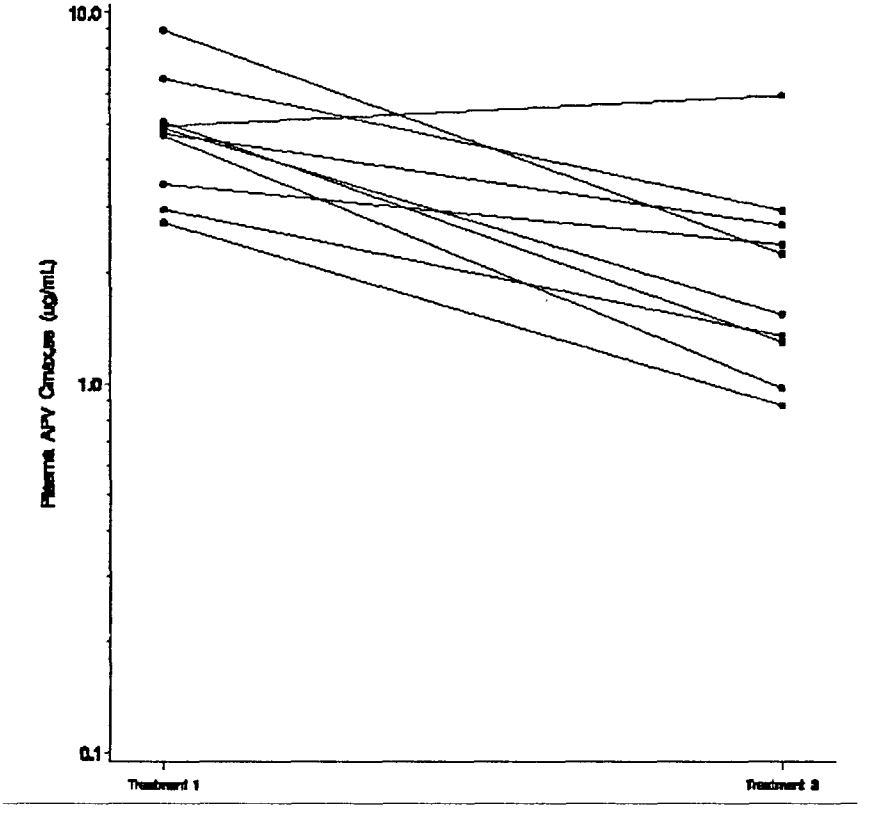
Treatment 1 = GW433908 700mg BID + RTV 100mg BID for 14 days

Treatment 3 = GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID (total of 200mg RTV BID) for 14 days

Figure 1. Comparative Semi-log Plot of Plasma APV PK Parameters vs. Treatment



Cmax (µg/mL)



APPEARS THIS WAY
ON ORIGINAL

Cτ (µg/mL)

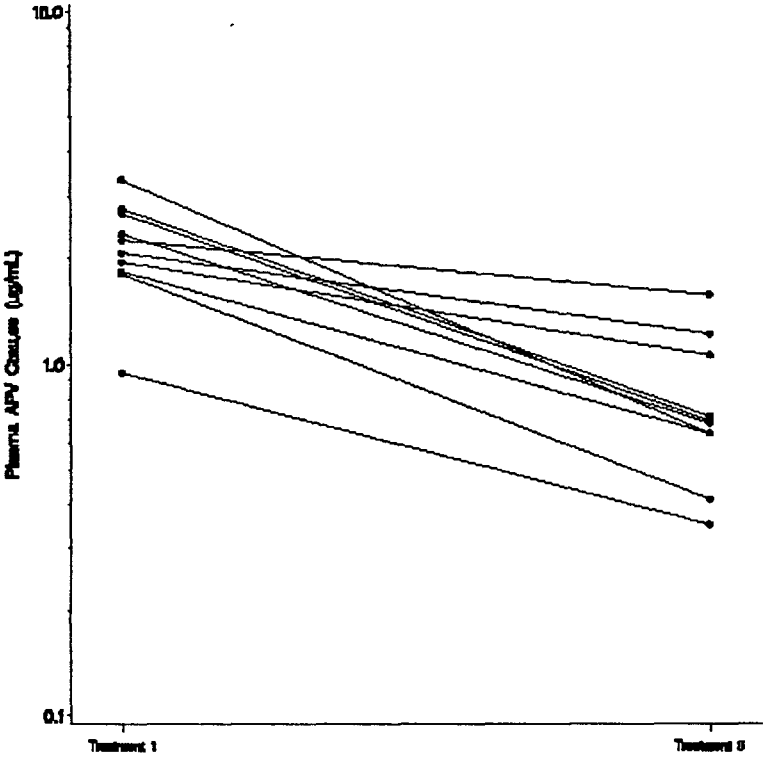


Table 3. Steady-State Plasma LPV PK Parameter Estimates, Geometric Mean (95% CI)

Plasma LPV PK Parameter	Treatment 2 Arms C & D (N=10)	Treatment 3 Arms C & D (N=10)
$AUC_{\tau,ss}$ (µg.h/mL)	81.9 (66.1-102)	112.0 (88.6-141.6)
$C_{max,ss}$ (µg/mL)	9.80 (8.30-11.59)	12.72 (10.04-16.12)
$C_{\tau,ss}$ (µg/mL)	5.34 (4.05-7.05)	8.14 (6.00-11.04)
$t_{max,ss}$ (h)[a]	4.00 (0.00-5.00)	4.00 (3.00-10.00)

a $t_{max,ss}$ data presented as median (range)
Treatment 2 = LPV 400mg/RTV 100mg BID for 14 days
Treatment 3 = GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID (total of 200mg RTV BID) for 14 days

Table 4. Steady-State Plasma LPV PK Treatment Comparisons, GLS Mean Ratio (90% CI)

Plasma LPV PK Parameter	Treatment 3/Treatment 2 Arms C & D (N=10)
$AUC_{\tau,ss}$ (µg.h/mL)	1.37 (1.20-1.55)
$C_{max,ss}$ (µg/mL)	1.30 (1.15-1.47)
$C_{\tau,ss}$ (µg/mL)	1.52 (1.28-1.82)
$t_{max,ss}$ (h)[a]	1.32 (0.92-1.71)

a LS mean ratio (90% CI) for $t_{max,ss}$

Treatment 2 = LPV 400mg/RTV 100mg BID for 14 days

Treatment 3 = GW433908 700mg BID + LPV 400mg/RTV 100mg BID + RTV 100mg BID (total of 200mg RTV BID) for 14 days

SAFETY RESULTS: GW433908/LPV/RTV combinations studied in APV10012 were poorly tolerated, with a high incidence and increased severity of adverse events. Thirteen of 36 (36%) subjects enrolled in APV10012 prematurely withdrew from the study due to adverse events; 10 of these subjects withdrew while taking the combination treatment. The most commonly reported drug-related adverse events were gastrointestinal symptoms (most notably diarrhea and nausea), fatigue, pruritus, rash, decreased appetite, oral/perioral numbness, dizziness, and disturbance of sense of taste. Elevations in serum triglyceride and/or cholesterol concentrations were observed.

CONCLUSIONS AND DISCUSSIONS: Coadminstration of LPV 400mg/RTV 100mg BID with GW433908 700mg BID + RTV 100mg BID significantly decreased plasma APV exposure (AUC decreased by 63%, Cmax decreased by 58%, and Cτ decreased by 65%). Coadminstration of LPV 400mg/RTV 100mg BID with GW433908 700mg BID + RTV 100mg BID significantly increased plasma LPV exposure (AUC increased by 37%, Cmax increased by 30%, and Cτ increased by 52%). Please refer to the review for study APV10011.

COMMENT TO THE SPONSOR: The mechanisms by which LPV/RTV markedly decreased plasma APV exposure need to be elucidated. Please refer to the review for study APV10011.

APV10013

TITLE: A Phase I, Randomized, Open Label, Three Period, Single Sequence, Steady State, Drug-Drug Interaction Study between Atorvastatin 10mg QD and GW433908 1400mg BID and between Atorvastatin 10mg QD and GW433908 700mg BID + Ritonavir 100mg BID in Healthy Adult Subjects

BACKGROUND: Based on the potential for elevated concentrations of statins via CYP3A4 inhibition, the AGENERASE product information does not recommend concomitant use of lovastatin or simvastatin and states that caution should be exercised when atorvastatin (ATO) or cerivastatin (recently removed from the US market by Bayer in August 2001) are coadministered with AGENERASE. Given the increased use of statins in the antiretroviral treated population, study APV10013 examined the interaction between GW433908 and ATO and between GW433908 + RTV and ATO. The effect of ATO on steady state plasma APV PK was also evaluated. In addition, single dose and steady state plasma APV PK were compared following administration of GW433908 and following administration of GW433908 + RTV. The

6β-hydroxycortisol/cortisol urine concentration ratios following single-dose and steady state administration of GW433908 1400mg BID were also compared for evaluation for potential autoinduction.

OBJECTIVES:

Primary:

- To compare steady state plasma ATO PK following administration of ATO 10mg QD with and without GW433908 1400mg BID.
- To compare steady state plasma ATO PK following administration of ATO 10mg QD with and without GW433908 700mg + RTV 100mg BID.
- To compare steady state plasma APV PK following administration of GW433908 1400mg BID with and without ATO 10mg QD.
- To compare steady state plasma APV PK following administration of GW433908 700mg BID + RTV 100mg BID with and without ATO 10mg QD.

Secondary:

- To assess 6β-hydroxycortisol/cortisol prior to dosing and following multiple-dose administration of GW433908 1400mg BID for 14 days.

SUBJECTS AND STUDY DESIGN: Phase I, randomized, open label, three-period, single-sequence, steady state, drug-drug interaction study conducted in healthy adult subjects at a single study center in the US. Thirty-two subjects were initially randomized to one of the following arms (16 per arm):

Arm	Sample Size	Period 1 Days 1-4	Washout 7-10 days	Period 2 Days 1-14	Period 3 Days 1-4
1	16	Treatment A		Treatment B	Treatment C
2	16	Treatment A		Treatment D	Treatment E

Treatment A = ATO 10mg QD for 4 days fasted[a]
Treatment B = GW433908 1400mg BID for 14 days fasted[a]
Treatment C = GW433908 1400mg BID + ATO 10mg QD for 4 days fasted[a]
Treatment D = GW433908 700mg/RTV 100mg BID for 14 days fasted[a]
Treatment E = GW433908 700mg/RTV 100mg BID + ATO 10mg QD for 4 days fasted[a]

a. Fasting for 8h prior to dosing and 4h post dosing for serial PK sampling occasions

On serial plasma PK sampling days (Period 1 Day 4, Period 2 Day 1, Period 2 Day 14, and Period 3 Day 4), subjects fasted for 8 hours prior to dosing and for an additional 4 hours post-dosing. In addition, subjects were required to fast for 8 hours before collection of single pre-dose plasma PK samples on Days 3, 6, 9, 12, and 13. Water was allowed ad libitum prior to dosing, and on serial plasma PK sampling days water was allowed ad libitum 2 hours after dosing.

Thirty-nine subjects were enrolled and twenty-six of the 39 subjects completed all three treatment periods (12 subjects in Arm 1 and 14 in Arm 2). The overall demographic characteristics of these were as following: Male (96%) and female (4%); White (50%) and Blacks (50%).

INVESTIGATOR AND STUDY LOCATION: [redacted]

FORMULATION: GW433908 700mg tablet (E01B212), NORVIR 100mg soft gelatin capsule, LIPITOR 10 mg oral tablets.

SAMPLE COLLECTION:

Pharmacokinetic Sampling Schedule

Time period	Analyte	Planned Time Relative to Dosing (hours)
Period 1		
Day 4	ATO + ATO metabolites[a]	0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose
Period 2		
Day –1	Urine 6β-hydroxycortisol/ cortisol (Arm 1 only)	0 (pre-dose), 0-6, 6-12, and 12-24 hours postdose
Day 1	APV	0 (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 postdose
Day 3	APV	0 (pre-dose)
Day 6	APV	0 (pre-dose)
Day 9	APV	0 (pre-dose)
Day 12	APV	0 (pre-dose)
Day 13	APV	0 (pre-dose)
Day 14	Urine 6β-hydroxycortisol/ cortisol (Arm 1 only)	0 (pre-dose), 0-6, 6-12, and 12-24 hours postdose
	APV	0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours postdose
Period 3		
Day 4	ATO + ATO metabolites[a]	0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose
	APV	0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours postdose

a metabolites = ortho- and para-hydroxy-atorvastatin

ASSAYS: Plasma samples were assayed for amprenavir at [redacted]. The plasma samples were assayed using a validated [redacted] method. Plasma PK samples were analyzed for ATO by [redacted] The plasma samples were assayed using a validated [redacted] method. The quality control samples had coefficients of variation less than or equal to [redacted] respectively for APV and ATO.

Urine samples were analyzed for 6β-hydroxycortisol and cortisol by [redacted] The urine samples were assayed by a validated method using [redacted] The lower limits of quantification, LLQ, were [redacted] for cortisol and [redacted] for 6β-hydroxycortisol. The quality control samples had coefficients of variation less than or equal to [redacted] respectively for cortisol and 6β-hydroxycortisol.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used [redacted] Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for AUC_{τ}, Cmax and C_{τ} were provided for each group.

PHARMACOKINETIC RESULTS:

Table 1. Single Dose Plasma APV PK Parameter Estimates, Geometric Mean (95% CI)

Plasma APV PK Parameter	Treatment B Arm 1 (N=12)	Treatment D Arm 2 (N=14)
AUC_{∞} (µg.h/mL)	19.5 (15.0-25.4)	41.2 (31.6-53.7)
AUC_{last} (µg.h/mL)	19.0 (14.7-24.7)	30.7 (25.6-36.7)
C_{max} (µg/mL)	4.00 (3.11-5.14)	4.14 (3.49-4.92)
C_{12} (µg/mL)	0.369 (0.254-0.536)	1.128 (0.922-1.380)
t_{max} (h)[a]	1.75 (0.75-5.00)	1.75 (1.00-2.50)
$t_{½}$ (h)	4.35 (3.46-5.48)	10.74 (8.29-13.91)
$AUC_{\%extrap}$ (µg.h/mL)	1.97 (1.22-3.20)	21.85 (16.73-28.54)
Arm 1 = Treatment A, washout, Treatment B, and Treatment C Arm 2 = Treatment A, washout, Treatment D, and Treatment E		
Treatment A = ATO 10mg QD for 4 days Treatment B = GW433908 1400mg BID for 14 days (results shown obtained from 1st dose) Treatment C = GW433908 1400mg BID + ATO 10mg QD for 4 days Treatment D = GW433908 700mg/RTV 100mg BID for 14 days (results shown obtained from 1st dose) Treatment E = GW433908 700mg/RTV 100mg BID + ATO 10mg QD for 4 days		

a. t_{max} data presented as median (range)

APPEARS THIS WAY
ON ORIGINAL

Table 2. Steady State Plasma APV PK Parameter, EstimatesGeometric Mean (95% CI)

Plasma APV PK Parameter	Treatment B Arm 1 (N=12)	Treatment C Arm 1 (N=12)	Treatment D Arm 2 (N=14)	Treatment E Arm 2 (N=14)
$AUC_{\tau,ss}$ (µg.h/mL)	17.0 (13.3-21.9)	12.4 (9.4-16.2)	27.8 (24.3-31.8)	27.6 (24.0-31.8)
$C_{max,ss}$ (µg/mL)	4.52 (3.41-6.00)	3.70 (2.80-4.89)	4.75 (4.07-5.55)	4.46 (3.93-5.05)
$C_{\tau,ss}$ (µg/mL)	0.23 (0.17-0.30)	0.20 (0.14-0.30)	1.53 (1.34-1.76)	1.55 (1.33-1.80)
$t_{max,ss}$ (h)[a]	1.75 (0.75-3.00)	1.25 (0.50-3.00)	1.50 (1.00-3.00)	1.50 (0.75-3.00)
R[b]	1.020 (0.759-1.370)	0.738 (0.611-0.892)	1.326 (1.158-1.518)	1.317 (1.158-1.498)
Arm 1 = Treatment A, washout, Treatment B, and Treatment C Arm 2 = Treatment A, washout, Treatment D, and Treatment E				
Treatment A = ATO 10mg QD for 4 days Treatment B = GW433908 1400mg BID for 14 days Treatment C = GW433908 1400mg BID + ATO 10mg QD for 4 days Treatment D = GW433908 700mg/RTV 100mg BID for 14 days Treatment E = GW433908 700mg/RTV 100mg BID + ATO 10mg QD for 4 days				

a. $t_{max,ss}$ data presented as median (range)

b. "R" denotes accumulation ratio = $AUC_{\tau,ss}/AUC_{12}$, where AUC_{12} = 12-h partial AUC from single dose.

Table 3. Steady State Plasma APV PK Treatment Comparisons, GLS Mean Ratio (90% CI)

Plasma APV PK Parameter	Geometric LS Mean				Ratio of GLS means (90% CI)	
	Arm 1		Arm 2		Arm 1	Arm 2
	Trt B (N=12)	Trt C (N=12)	Trt D (N=14)	Trt E (N=14)	C/B	E/D
$AUC_{\tau,ss}$ (µg.h/mL)	17.04	12.36	27.82	27.62	0.73 (0.59-0.88)	0.99 (0.93-1.06)
$C_{max,ss}$ (µg/mL)	4.52	3.70	4.75	4.46	0.82 (0.66-1.01)	0.94 (0.88-1.00)
$C_{\tau,ss}$ (µg/mL)	0.23	0.20	1.53	1.55	0.88 (0.73-1.06)	1.01 (0.96-1.06)
$t_{max,ss}$ (h)[a]	1.81	1.46	1.57	1.48	0.80 (0.50-1.11)	0.94 (0.69-1.20)
Arm 1 = Treatment A, washout, Treatment B, and Treatment C Arm 2 = Treatment A, washout, Treatment D, and Treatment E						
Treatment A = ATO 10mg QD for 4 days Treatment B = GW433908 1400mg BID for 14 days Treatment C = GW433908 1400mg BID + ATO 10mg QD for 4 days Treatment D = GW433908 700mg/RTV 100mg BID for 14 days Treatment E = GW433908 700mg/RTV 100mg BID + ATO 10mg QD for 4 days						

a. Ratio of LS means (90% CI) for $t_{max,ss}$

Table 4. Steady State Plasma ATO PK Parameter Estimates, Geometric Mean (95% CI)

Plasma ATO PK Parameter	Treatment A Arm 1 (N=12)	Treatment A Arm 2 (N=14)	Treatment C Arm 1 (N=12)	Treatment E Arm 2 (N=14)
$AUC_{\tau,ss}$ (ng.h/mL)	16.49 (13.05-20.83)	16.25 (12.60-20.97)	37.89 (30.01-47.85)	41.18 (31.73-53.43)
$C_{max,ss}$ (ng/mL)	2.67 (1.98-3.60)	2.66 (1.89-3.74)	10.79 (7.84-14.83)	7.54 (5.13-11.08)
$C_{\tau,ss}$ (ng/mL)	0.393 (0.300-0.514)	0.390 (0.289-0.527)	0.354 (0.269-0.466)	0.677 (0.548-0.836)
$t_{max,ss}$ (h)[a]	0.88 (0.50-6.00)	0.75 (0.25-2.00)	1.25 (0.75-3.00)	1.00 (0.50-3.00)
Arm 1 = Treatment A, washout, Treatment B, and Treatment C Arm 2 = Treatment A, washout, Treatment D, and Treatment E				
Treatment A = ATO 10mg QD for 4 days Treatment B = GW433908 1400mg BID for 14 days Treatment C = GW433908 1400mg BID + ATO 10mg QD for 4 days Treatment D = GW433908 700mg/RTV 100mg BID for 14 days Treatment E = GW433908 700mg/RTV 100mg BID + ATO 10mg QD for 4 days				

a. t_{max} data presented as median (range)

Table 5. Plasma ATO PK Treatment Comparisons Ratio of GLS means (90% CI)

Plasma ATO PK Parameter	Geometric LS Mean				Ratio of GLS means (90% CI)	
	Arm 1		Arm 2		Arm 1	Arm 2
	Trt A (N=12)	Trt C (N=12)	Trt A (N=14)	Trt E (N=14)	C/A	E/A
$AUC_{\tau,ss}$ (µg.h/mL)	16.49	37.89	16.25	41.18	2.30 (2.00-2.64)	2.53 (2.15-2.99)
$C_{max,ss}$ (µg/mL)	2.668	10.787	2.657	7.542	4.04 (3.05-5.37)	2.84 (2.26-3.57)
$C_{\tau,ss}$ (µg/mL)	0.393	0.354	0.390	0.677	0.90 (0.73-1.12)	1.73 (1.45-2.08)
$t_{max,ss}$ (h)[a]	1.48	1.50	0.75	1.25	1.01 (0.38-1.65)	1.67 (1.24-2.09)
Arm 1 = Treatment A, washout, Treatment B, and Treatment C Arm 2 = Treatment A, washout, Treatment D, and Treatment E						
Treatment A = ATO 10mg QD for 4 days Treatment B = GW433908 1400mg BID for 14 days Treatment C = GW433908 1400mg BID + ATO 10mg QD for 4 days Treatment D = GW433908 700mg/RTV 100mg BID for 14 days Treatment E = GW433908 700mg/RTV 100mg BID + ATO 10mg QD for 4 days						

a. Ratio of LS means (90% CI) for t_{max}

Table 6. Plasma APV PK Comparisons: Steady State/Single Dose

Plasma APV PK Parameter	Geometric LS Mean				Ratio of GLS means (90% CI)	
	Arm 1 (Trt B) (N=12)		Arm 2 (Trt D) (N=14)		Trt B	Trt D
	Day 1	Day 14	Day 1	Day 14	Day 14/Day 1	Day 14/Day 1
AUC(μg.h/mL) AUC_{∞} (Day 1), $AUC_{\tau,ss}$ (Day 14);	19.50	17.04	41.19	27.82	0.87 (0.70-1.10)	0.68 (0.56-0.81)
C_{max}(μg/mL) C_{max} (Day 1), $C_{max,ss}$ (Day 14);	4.00	4.52	4.14	4.75	1.13 (0.92-1.38)	1.15 (1.02-1.29)
C_{τ}(μg/mL) C_{12} (Day 1), $C_{\tau,ss}$ (Day 14)	0.37	0.23	1.13	1.53	0.62 (0.53-0.72)	1.36 (1.16-1.59)
Arm 1 = Treatment A, washout, Treatment B, and Treatment C Arm 2 = Treatment A, washout, Treatment D, and Treatment E						
Treatment A = ATO 10mg QD for 4 days Treatment B = GW433908 1400mg BID for 14 days Treatment C = GW433908 1400mg BID + ATO 10mg QD for 4 days Treatment D = GW433908 700mg/RTV 100mg BID for 14 days Treatment E = GW433908 700mg/RTV 100mg BID + ATO 10mg QD for 4 days						

Table 7. Urinary 6β-hydroxycortisol/cortisol ratio Comparison: Day 14/ Day -1

Parameter	Geometric LS Mean		Ratio of GLS Means (90% CI)
	Day -1 (N=12)	Day 14 (N=12)	Day 14/Day -1
6β-hydroxycortisol/cortisol Ratio	6.90	5.90	0.86 (0.72-1.02)

SAFETY RESULTS: No serious adverse events or deaths were reported during this study.

CONCLUSIONS AND DISCUSSIONS:

Co-administration of GW433908 1400mg BID with ATO 10mg QD resulted in reductions of APV Cmax and AUC by 18% and 27%, respectively. Co-administration of GW433908 700mg + ritonavir (RTV) 100mg BID with ATO 10mg QD showed no effect on APV pharmacokinetics. The potential mechanisms are not known.

Co-administration of ATO 10mg QD with GW433908 1400mg BID resulted in increases in ATO Cmax and AUC and by approximately 4.0 fold and 2.3 fold, respectively. Co-administration of ATO 10mg QD with GW433908 700mg + RTV 100mg BID resulted in increases of ATO Cmax and AUC by approximately 2.8 fold and 2.5 fold, respectively.

APV AUC was reduced by 13% from Day 1 after administration of GW433908 1400mg BID for 14 days and by 32% after administration of GW433908 700mg + RTV 100mg BID for 14 days.

BEST POSSIBLE COPY

BEST POSSIBLE COPY

Evaluation of the urinary 6β-hydroxycortisol/cortisol ratio before and after two weeks of GW433908 1400mg BID dosing showed a 14% reduction in this ratio following multiple-dose administration. It seems that GW433908 administered at a dose of 1400mg BID is not a potent CYP3A4 inducer based on the average 14% decrease in the 24-hour urinary 6β hydroxycortisol/cortisol concentration ratio, a marker of CYP3A4-induction.

We will recommend use lower dose (< 20 mg/day) of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors that are not extensively metabolized by CYP3A4, such as pravastatin or fluvastatin or rosuvastatin in combination with fosamprenavir.

APV100015

TITLE: A Pivotal, Phase I, Single-Dose, Open-Label, Randomized, Three Period, Balanced Crossover Study to Assess the Bioequivalence of GW433908 Oral Film-coated 700mg Tablet Formulations in Healthy Adult Subjects

BACKGROUND: GW433908 pivotal Phase III studies were initiated with 465mg and 700mg oral film-coated tablets manufactured with [redacted] drug substance manufactured at [redacted] scale. The 465mg oral film-coated tablets were manufactured at [redacted] and the 700mg oral film-coated tablets were manufactured at [redacted] scale. The bioequivalence of the 465mg and 700mg oral film-coated tablet strengths was established [APV10006]. After initiating the GW433908 Phase III development program, the manufacturing processes for both GW433908 drug substance and drug product were [redacted] and [redacted] of drug substance was introduced. This study, APV10015, assessed the bioequivalence of GW433908 oral film-coated 700mg tablet variants administered in the pivotal GW433908 Phase III studies (Tablets A, B and C), including the intended market product (Tablet C). The formulation of the tablets was the same; however, the drug substance and drug product manufacturing scales and the [redacted] differed. Tablet A was manufactured at [redacted] scale with [redacted] drug substance manufactured at [redacted] scale. Tablet B was manufactured at [redacted] scale with [redacted] drug substance manufactured at [redacted] scale. Tablet C was manufactured at [redacted] scale with [redacted] drug substance manufactured at [redacted] scale.

OBJECTIVES: The primary objective was to assess the bioequivalence of the three GW433908 oral film-coated 700mg tablet variants administered in the pivotal GW433908 studies (Treatments A, B, and C), including the intended market product (Treatment C) in the fasted state. The secondary objective was to assess the safety and tolerability of single 1400mg doses of the three GW433908 oral film-coated 700mg tablet variants in the fasted state.

SUBJECTS AND STUDY DESIGN: APV10015 was a pivotal, Phase I, single-dose, open-label, randomized, three period, balanced crossover study conducted at a single study center in the US. Subjects were randomized using a balanced 3 x 3 Williams design to one of the following six treatment sequences:

Treatment Sequence	Sample Size	Period 1	Period 2	Period 3
1	6	Treatment A	Treatment B	Treatment C
2	6	Treatment C	Treatment A	Treatment B
3	6	Treatment B	Treatment C	Treatment A
4	6	Treatment C	Treatment B	Treatment A
5	6	Treatment B	Treatment A	Treatment C
6	6	Treatment A	Treatment C	Treatment B

Treatment A = Two GW433908 oral film-coated 700mg tablets [a], [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted
Treatment B = Two GW433908 oral film-coated 700mg tablets [a], [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted
Treatment C = Two GW433908 oral film-coated 700mg tablets [a], [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted

There was a washout period of 4 to 7 days between doses. Subjects were required to fast 10 hours before administration of each dose. Water was permitted during the fast. Subjects fasted for an additional 4h after each dose administration. Water was permitted beginning 2 hours after dosing.

Thirty-six subjects were enrolled and thirty-two of these 36 subjects completed the study. The demographic characteristics of these were as following: Male (78%) and female (22%); White (56%), Black (39%) and Hispanics (6%).

INVESTIGATOR AND STUDY LOCATION: GlaxoSmithKline Clinical Pharmacology Unit, Presbyterian Medical Center, University of Pennsylvania Health System

FORMULATION:

Investigational product	Dosage Form	Drug Substance and Tablet Manufacturing Scale and use of Milling	Batch Number
GW433908	700mg Oral Film-coated Tablet	[redacted] drug substance, [redacted] scale tablet, [redacted] scale	E00B222
GW433908	700mg Oral Film-coated Tablet	[redacted] drug substance, [redacted] scale tablet, [redacted] scale	B044089
GW433908	700mg Oral Film-coated Tablet	[redacted] drug substance, [redacted] scale Tablet [redacted] scale	B048577

SAMPLE COLLECTION: Blood samples for measurement of APV concentrations were collected prior to the dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dose administration in each of the three periods.

ASSAY: Plasma PK samples were analyzed for APV by [redacted] The method was validated for the determination of APV in human plasma using [redacted]
The quality control samples had coefficients of variation less than or equal to [redacted] for APV.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax, AUC (Tlast) and AUC(INF) were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACOKINETIC RESULTS:

Table 1. Plasma APV PK Parameter Estimates

Parameter	Geometric Mean (95% CI) Treatment A	Treatment B	Treatment C
AUC_{∞} (µg.h/mL)	17.7 (15.2-20.6)	15.3 (13.3-17.6)	14.8 (12.8-17.2)
AUC_{last} (µg.h/mL)	17.0 (14.7-19.7)	14.8 (12.9-17.0)	14.3 (12.4-16.5)
C_{max} (µg/mL)	4.07 (3.44-4.81)	3.79 (3.36-4.27)	3.41 (2.87-4.04)
t_{max} (h) [a]	1.50 (0.75-5.97)	1.48 (0.52-3.98)	1.50 (0.50-6.02)

Treatment A = Two GW433908 oral film-coated 700mg tablets, [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted

Treatment B = Two GW433908 oral film-coated 700mg tablets, [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted

Treatment C = Two GW433908 oral film-coated 700mg tablets, [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted

[a] Values for t_{max} denote median (range)

Table 2. Plasma APV PK Treatment Comparisons

PK Parameter	Geometric LS Mean Treatment A	Treatment B	Treatment C	Ratio of the GLS Means (90% CI) B/A	C/A
AUC_{∞} (µg.h/mL)	17.69	15.39	14.80	0.870 (0.794-0.953)	0.837 (0.764-0.917)
AUC_{last} (µg.h/mL)	16.89	14.70	14.17	0.870 (0.793-0.955)	0.839 (0.764-0.921)
C_{max} (µg/mL)	4.02	3.74	3.37	0.932 (0.816-1.064)	0.839 (0.734-0.958)

Treatment A = Two GW433908 oral film-coated 700mg tablets, [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted

Treatment B = Two GW433908 oral film-coated 700mg tablets, [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted

Treatment C = Two GW433908 oral film-coated 700mg tablets [redacted] drug substance manufactured at [redacted] scale and tablets manufactured at [redacted] scale, fasted

Treatment B achieved equivalent plasma APV Cmax values and lower AUClast and AUC∞ values relative to Treatment A. The ratio of the GLS means (90% CI) for Cmax was 0.932 (0.816 - 1.064), for AUClast was 0.870 (0.793 - 0.955) and for AUC was 0.870 (0.794 - 0.953). Treatment C achieved lower plasma APV Cmax, AUClast and AUC values relative to Treatment A. The ratio of the GLS means (90% CI) for Cmax was 0.839 (0.734 - 0.958), for AUClast was 0.839 (0.764 - 0.921) and for AUC was 0.837 (0.764 - 0.917).

SAFETY RESULTS: All AEs, with the exception of three that were moderate and one that was severe (severe toothache), were considered mild in intensity. No serious adverse events or deaths were reported during this study.

CONCLUSIONS AND DISCUSSION: Both tablet variants B and C are not bioequivalent to tablet variant A. For tablet variant B, AUC was 13% lower than that of tablet variant A. For tablet variant C, both AUC and C_{max} were 16% lower than those of tablet variant A. Reasons are not clear for the decreased bioavailability of tablet variants B and C.

APV100021

TITLE: Pivotal, Phase I, Single-Dose, Open-Label, Randomized, Two-Period, Balanced Crossover Study to Assess the Bioequivalence of GW433908 Oral Film-Coated 700mg Tablets in Healthy Adult Subjects

BACKGROUND: A Phase I study in healthy adult subjects, APV10015, assessed the bioequivalence of GW433908 oral film-coated 700mg tablet variants administered in the pivotal GW433908 Phase III studies (Variants A, B, and C), including the tablet variant (Variant C) originally intended for the market. The formulation of the tablets was the same; however, the drug substance and drug product manufacturing scales and the [redacted] differed. APV10015 demonstrated that Variants B and C delivered lower plasma APV concentrations and were not bioequivalent to Variant A. At this time, the sponsor plans to market variant A. Because in vitro testing did not predict the results of the failed bioequivalence study, this study, APV10021, was initiated to demonstrate bioequivalence between the proposed commercial GW433908 oral film-coated 700mg Variant A tablet and the Variant A tablet used to initiate the pivotal Phase III studies.

OBJECTIVES: The primary objectives were to assess the bioequivalence of the proposed commercial GW433908 oral film-coated 700mg tablets and tablets used to initiate the pivotal Phase III studies. The secondary objectives were to summarize GW433908 concentrations following administration of single 1400mg doses of GW433908 oral film-coated 700mg tablets and to assess the safety and tolerability of single 1400mg doses of GW433908 oral film-coated 700mg tablets.

SUBJECTS AND STUDY DESIGN: Protocol APV10021 was a pivotal, Phase I, single-dose, open-label, randomized, two-period, balanced crossover study conducted at two study centers in the US. Eighty healthy adult subjects were enrolled to obtain 68 evaluable subjects. If more than 12 subjects withdrew from the study before completing both periods, additional subjects were to be enrolled as replacement subjects to attain the 68 evaluable subjects. Subjects were randomized to one of the following two treatment sequences:

Treatment Sequence	Sample Size	Period 1	Period 2
1	40	Treatment A	Treatment B
2	40	Treatment B	Treatment A
Treatment A: Two GW433908 700mg[a] oral film-coated tablets used to initiate pivotal Phase III studies (Variant A, Batch E00B149).			
Treatment B: Two GW433908 700mg[a] oral film-coated proposed commercial tablets (Variant A, Batch B083969).			

[a] Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.

For each of the two treatment visits, subjects checked into the study center on the day prior to dosing and completed the check-in assessments. Prior to dosing and for 24 hours following each dosing, the subjects underwent safety assessments and plasma pharmacokinetic (PK) sampling. There was a washout period of 4 to 7 days between doses. Subjects returned to the study center for a follow-up visit within 4 to 7 days after completing the last treatment assessments or withdrawing from the study. Subjects were required to fast 10 hours before administration of study drug. Water was permitted during the fast. Subjects fasted for an additional 4h after dosing. Water was permitted 2 hours after dosing.

Eighty subjects were enrolled and seventy-eight of these 80 subjects completed the study. The demographic characteristics of these were as following: Male (54%) and female (46%); White (64%), Hispanics (25%), Black (10%) and Asian (1%).

INVESTIGATOR AND STUDY LOCATION: Two study centers in the US

FORMULATION: Treatment A: Two GW433908 700mg oral film-coated tablets used to initiate pivotal Phase III studies (Variant A, Batch E00B149). Treatment B: Two GW433908 700mg oral film-coated proposed commercial tablets (Variant A, Batch B083969).

SAMPLE COLLECTION: Blood samples were collected for assay of APV and GW433908 concentrations over 24h during each period prior to the dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours post dose.

ASSAY: Samples were stored at -20°C until analyzed. Samples were assayed for APV and GW433908 concentrations by the Department of Worldwide Bioanalysis, DMPK, GSK R&D, King of Prussia, PA using [redacted]. The lower limits of quantification (LLQ) were [redacted] and [redacted] for amprenavir and GW433908, respectively, using a 200 µL aliquot of plasma. The quality control samples had coefficients of variation less than or equal to [redacted] for APV.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax, AUC (Tlast) and AUC(INF) were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACOKINETIC RESULTS:

Table 1. Summary of Plasma APV Pharmacokinetic Parameter Estimates in APV10021

Parameter	Treatment A (Phase III Tablet) (n=78)	Treatment B (Proposed Commercial Tablet) (n=78)
AUC_{∞} (µg•h/mL)	23.74 (21.46-26.28)[a]	24.05 (21.83-26.50)[b]
AUC_{last} (µg•h/mL)	22.45 (20.27-24.87)	23.12 (21.01-25.45)
C_{max} (µg/mL)	5.14 (4.66-5.68)	5.41 (4.96-5.91)
$t_{½}$ (h)	4.64 (4.16-5.18)[a]	4.45 (3.98-4.96)[b]
t_{max} (h)	1.50 (0.50-8.00)	1.50 (0.50-8.00)
$AUC_{\%extrap}$ (µg•h/mL)	2.21 (0.12-24.53)[a]	2.30 (0.11-22.6)[b]
t_{lag} (h)	0.00 (0.00-0.50)	0.00 (0.00-0.50)

Treatment A: Two GW433908 700mg[c] oral film-coated tablets used to initiate pivotal Phase III studies (Variant A, Batch E00B149).
Treatment B: Two GW433908 700mg[c] oral film-coated proposed commercial tablets (Variant A, Batch B083969).

Data presented as geometric mean (95% confidence interval) except for t_{max}, $AUC_{\%extrap}$ and t_{lag}, which are presented as median (range).

a. n=76, as λ_z could not be estimated for all subjects (see text).
b. n=75, as λ_z could not be estimated for all subjects (see text).
c. Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.

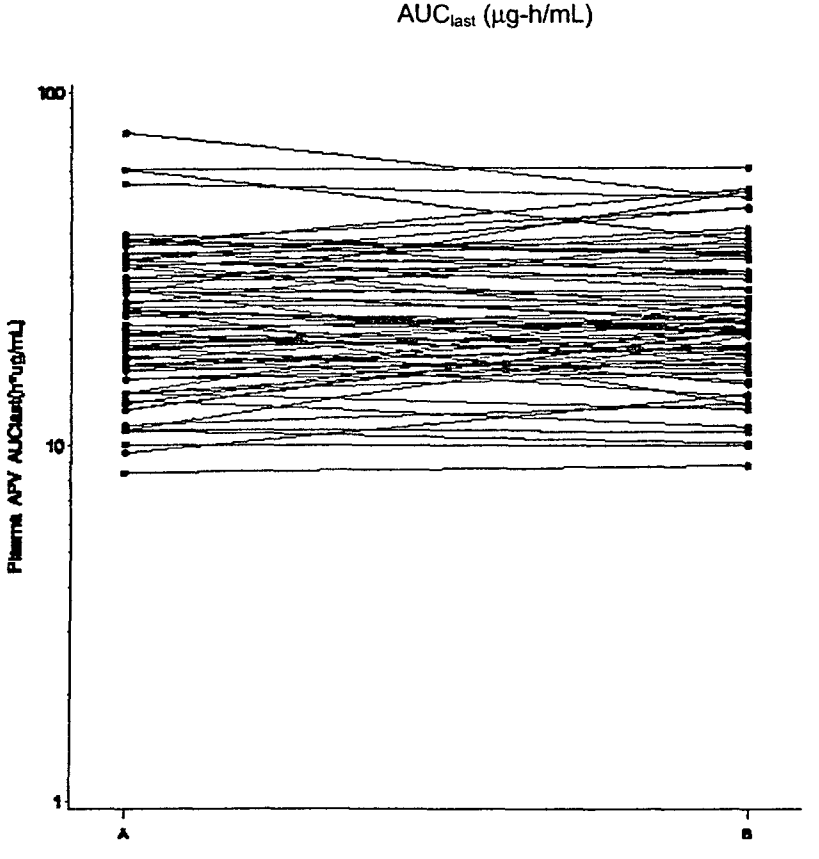
BEST POSSIBLE COPY

Table 2. Summary of Plasma GW433908 Pharmacokinetic Parameter Estimates in APV10021

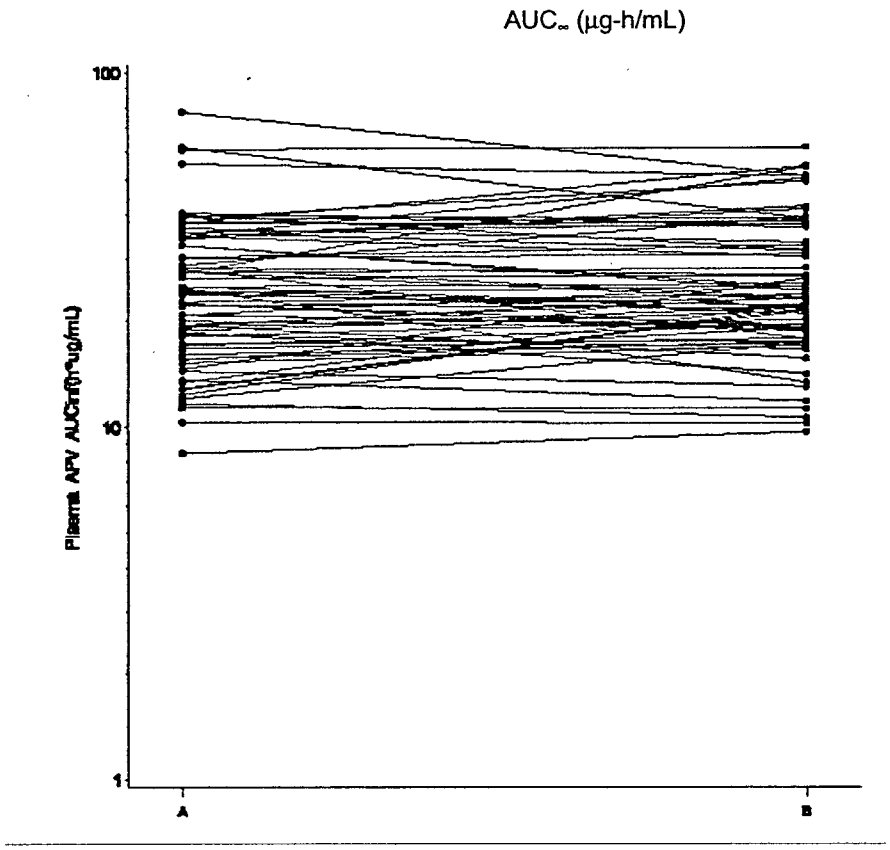
Parameter	N	Treatment A (Phase III Tablet)	N	Treatment B (Proposed Commercial Tablet)
AUC_{last} (µg•h/mL)	41	0.02 (0.02-0.03)	40	0.02 (0.02-0.03)
C_{max} (µg/mL)	62	0.016 (0.013-0.019)	67	0.014 (0.012-0.016)
t_{max} (h)	62	0.94 (0.25-12.03)	67	1.00 (0.25-10.00)

Treatment A: Two GW433908 700mg[a] oral film-coated tablets used to initiate pivotal Phase III studies (Variant A, Batch E00B149).
Treatment B: Two GW433908 700mg[a] oral film-coated proposed commercial tablets (Variant A, Batch B083969).
Data presented as geometric mean (95% confidence interval) except for t_{max} which is presented as median (range).
a. Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.

Figure 1. Comparative Semi-log Plot of Plasma APV PK Parameters vs Treatments

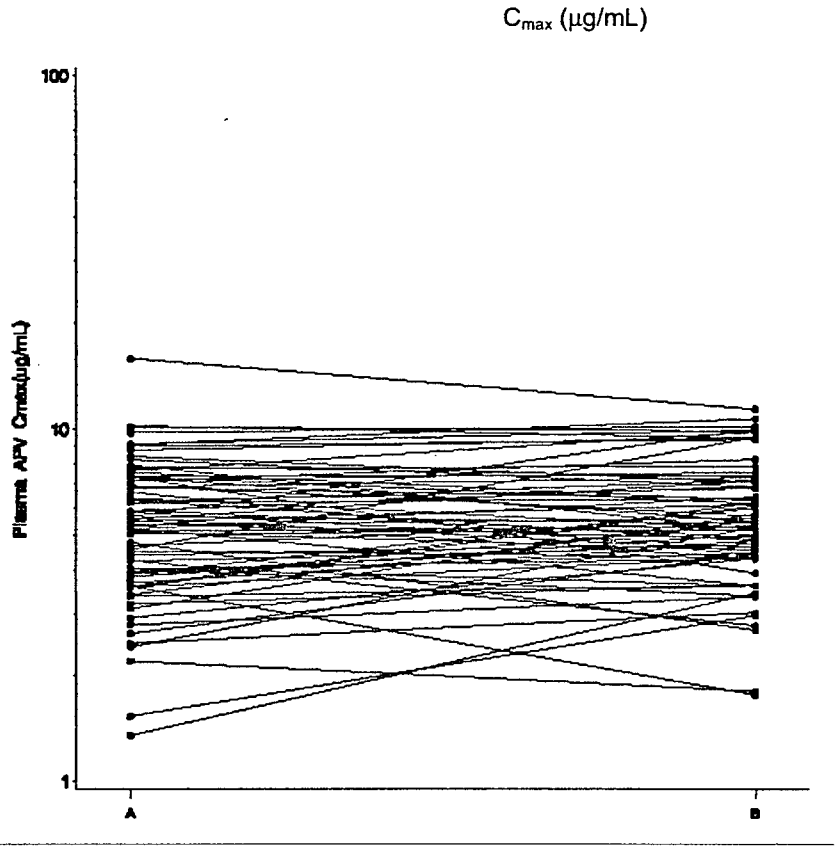


BEST POSSIBLE COPY



APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY



BEST POSSIBLE COPY

Table 3. Summary of the Bioequivalence Analysis in APV10021

	GLS Mean N=78		Ratio of GLS Means (90% CI)
Plasma APV PK Parameter	Treatment A (Phase III Tablet)	Treatment B (Proposed Commercial Tablet)	Treatment B/A
AUC_{∞} (µg•h/mL)	23.76	24.12	1.02 (0.97-1.06)
AUC_{last} (µg•h/mL)	22.51	23.05	1.02 (0.98-1.07)
C_{max} (µg/mL)	5.15	5.38	1.04 (0.98-1.11)
Treatment A: Two GW433908 700mg[a] oral film-coated tablets used to initiate pivotal Phase III studies (Variant A, Batch E00B149). Treatment B: Two GW433908 700mg[a] oral film-coated proposed commercial tablets (Variant A, Batch B083969).			

a. Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.

SAFETY RESULTS: The most commonly reported AEs were headache (18%), nausea (18%), lightheadedness (8%), and dizziness (5%). All other AEs occurred in ≤4% of subjects. AE occurrence rates were similar for both treatments. All AEs were mild or moderate in intensity. No severe AEs were reported.

CONCLUSIONS AND DISCUSSION: The study design is acceptable. Based on the ratio of the GLS means and associated 90% CI for AUClast, AUC and Cmax data, the rate and extent of bioavailability of APV was similar following administration of the GW433908 proposed commercial tablets and the

GW433908 tablets used to initiate the pivotal Phase III trials. Bioequivalence was demonstrated for the proposed commercial tablets and the tablets used to initiate the pivotal Phase III studies. Plasma concentrations of the pro-drug, GW433908, were negligible and similar after administration of the two treatments.

APV100022

TITLE: A Phase I, Randomized, Open Label, Two-Period, Four-Arm, Balanced Cross-Over, Steady-State, Drug Interaction Study between Ritonavir 100mg BID and GW433908 700mg BID and between Ritonavir 100mg BID and AGENERASE 600mg BID in Healthy Adult Subjects

BACKGROUND: This study was designed to assess the effect of RTV 100mg BID on plasma APV PK following co administration with GW433908 700mg BID and following co-administration with AGN 600mg BID. Although the AGN/RTV interaction has already been evaluated, this interaction was included to allow a comparison of RTV effects on GW433908 versus AGN under identical conditions (same study population and same PK sampling scheme). When cross-study comparisons are made between comparable GW433908/RTV and AGN/RTV regimens, plasma APV exposures are similar, suggesting that RTV has similar effects on plasma APV PK when co-administered with either GW433908 or AGN; however, these comparisons include data from both healthy and HIV-infected subjects and utilize different plasma PK sampling schemes. Results from this study may allow extrapolation of drug interaction information from AGENERASE label to the Lexiva label.

OBJECTIVES: The primary objectives were to compare plasma APV PK following administration of AGN 600mg BID with and without RTV 100mg BID, and to compare plasma APV PK following administration of GW433908 700mg BID with and without RTV 100mg BID. The secondary objectives were to explore the relative effects of RTV on plasma APV PK following co-administration with AGN and following co-administration with GW433908, to describe plasma GW433908 PK following administration of GW433908 700mg BID with and without RTV 100mg BID, and to assess the safety and tolerability of AGN 600mg BID and GW433908 700mg BID when each drug is administered with and without RTV 100mg BID.

SUBJECTS AND STUDY DESIGN: Protocol APV10022 was a phase I, randomized, open label, two-period, four-arm, balanced cross-over, steady-state, drug interaction study conducted in healthy adult subjects at a single study center in the US. Thirty-two subjects were planned to be randomized to one of the following arms:

Arm	Sample Size	Period 1 Days 1-14	Washout 28-36 days	Period 2 Days 1-14
1	8	Treatment A		Treatment B
2	8	Treatment B		Treatment A
3	8	Treatment C		Treatment D
4	8	Treatment D		Treatment C

Treatment A = AGN 600 mg BID for 14 days.
Treatment B = AGN 600 mg BID + RTV 100 mg BID for 14 days.
Treatment C = GW433908 700 mg[a] BID for 14 days.
Treatment D = GW433908 700 mg[a] BID + RTV 100 mg BID for 14 days

a. Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.

Subjects were required to fast for 10 hours before administration of the morning dose of study drug on the serial PK sampling day (Day 14) and before collection of pre-dose trough APV PK samples on Days 3, 6,

9, 12, and 13 of each period. Water was permitted during the fast. Subjects fasted for an additional 4h after dosing on Day 14 of Periods 1 and 2.

Thirty-six subjects were enrolled and twenty-six of the 36 subjects completed the treatment periods (15 subjects in Arms 1 and 2, 11 in Arms 3 and 4). The overall demographic characteristics of these were as following: Male (69%) and female (31%); White (56%), Hispanics (22%), Black (16%) and Asians (6%).

INVESTIGATOR AND STUDY LOCATION:

FORMULATION: GW433908, 700mg tablet (E00B149); AGN capsules, 150mg; NORVIR soft gelatin capsules, 100 mg

SAMPLE COLLECTION: Blood samples were collected for assay of APV and GW433908 concentrations over 12h during each period prior to the dose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours post dose on Day 14. Additional samples were collected on Days 3, 6, 9, 12, and 13 prior to the morning dose (at time 0).

ASSAY: Samples were analyzed for APV and GW433908 concentrations by using a validated method The quality control samples had coefficients of variation less than or equal to respectively for APV and GW433908.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used (Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax and AUCτ were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACOKINETIC RESULTS:

Table 1. Plasma APV PK Parameter Summary for APV10022

	Geometric Mean (95% CI)			
Plasma APV PK Parameter	**Treatment A (AGN) N=11**	**Treatment B (AGN+RTV) N=11**	**Treatment C (GW433908) N=15**	**Treatment D (GW433908+RTV) N=15**
$AUC_{\tau,ss}$ (µg•h/mL)	8.21 (6.38-10.6)	26.2 (22.3-30.9)	9.51 (7.81-11.6)	33.2 (28.0-39.5)
$C_{max,ss}$ (µg/mL)	3.66 (2.76-4.84)	4.69 (3.97-5.54)	3.19 (2.64-3.85)	4.92 (4.19-5.77)
$C_{\tau,ss}$ (µg/mL)	0.122 (0.071-0.207)	1.32 (1.11-1.57)	0.135 (0.099-0.183)	1.77 (1.48-2.13)
$t_{max,ss}$[b] (h)	0.75 (0.50-1.50)	1.00 (0.75-1.50)	1.00 (0.50-3.00)	1.50 (0.75-4.00)

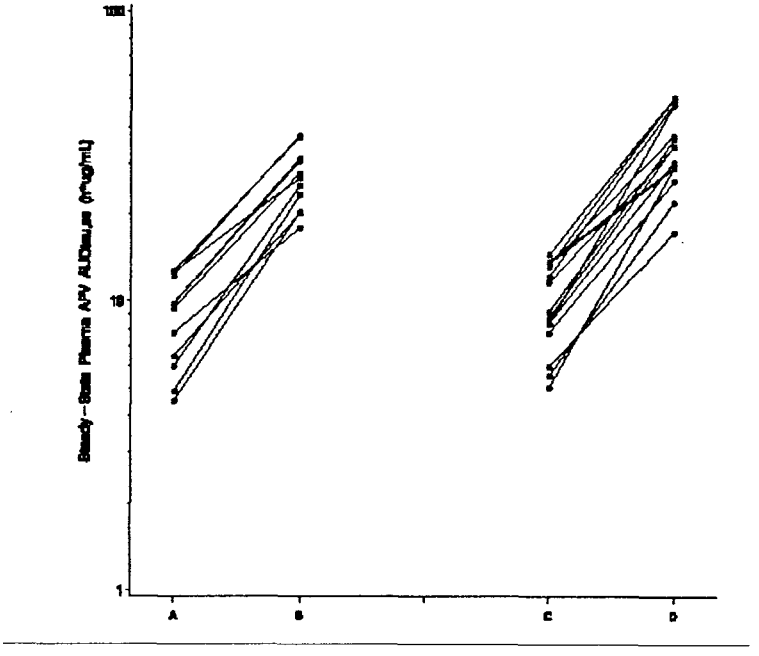
Treatment A = AGN 600 mg BID for 14 days.
Treatment B = AGN 600 mg BID + RTV 100 mg BID for 14 days.
Treatment C = GW433908 700 mg[a] BID for 14 days.
Treatment D = GW433908 700 mg[a] BID + RTV 100 mg BID for 14 days

a. Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.
b. t_{max} was median and range.

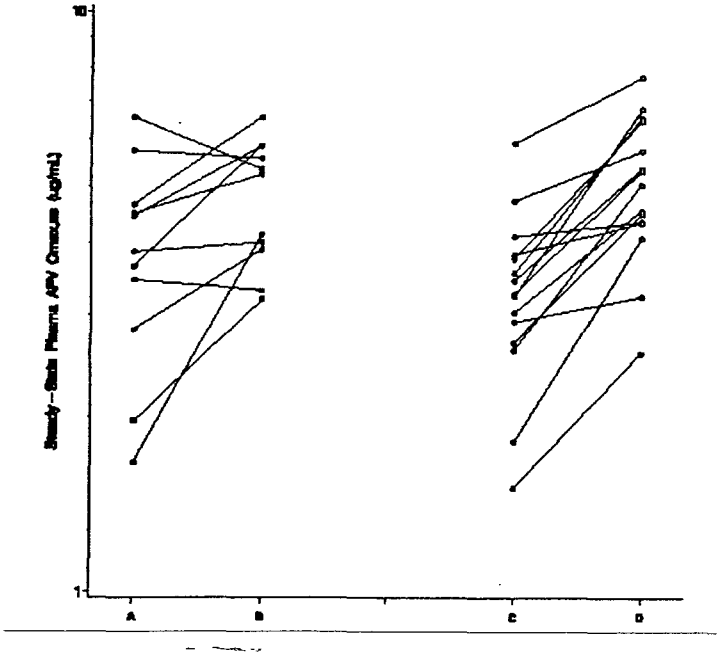
BEST POSSIBLE COPY

Figure 1. Comparative Semi-log Plot of Plasma APV PK Parameters vs Treatments

$AUC_{\tau,ss}$ (µg-h/mL)



C_{max} (µg/mL)



BEST POSSIBLE COPY

$C_{\tau,ss}$ (µg/mL)

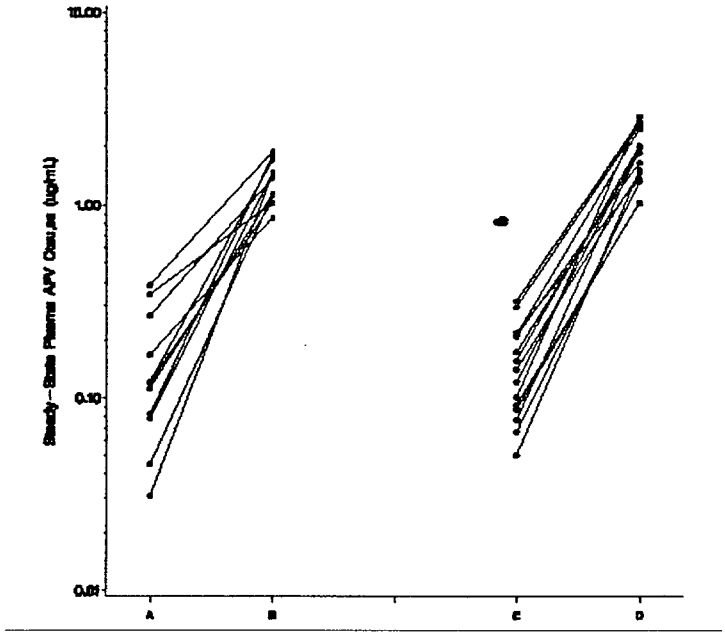


Table 2. Drug Interaction Analysis for APV10022

Plasma APV Parameter	GLS Mean				Ratio of GLS Means (90% CI)	
	Treatment					
	A N=11	B N=11	C N=15	D N=15	B : A	D : C
$AUC_{\tau,ss}$ (ug•h/mL)	8.65	27.35	9.31	31.70	3.16 (2.83-3.53)	3.40 (3.09-3.75)
$C_{max,ss}$ (ug/mL)	3.80	4.82	3.14	4.75	1.27 (1.11-1.46)	1.51 (1.34-1.70)
$C_{\tau,ss}$ (ug/mL)	0.13	1.41	0.13	1.65	10.73 (7.82-14.73)	12.68 (9.67-16.64)
$t_{max,ss}$ (h)[a]	0.92	1.00	1.36	1.74	1.08 (0.60-1.56)	1.28 (0.60-1.77)

Treatment A = AGN 600 mg BID for 14 days.
Treatment B = AGN 600 mg BID + RTV 100 mg BID for 14 days.
Treatment C = GW433908 700 mg[b] BID for 14 days.
Treatment D = GW433908 700 mg[b] BID + RTV 100 mg BID for 14 days.

a. LS mean ratio for comparison
b. Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.

Table 3. Relative Effect of RTV on Plasma APV PK when Coadministered with GW433908 versus AGN for APV10022

Plasma APV PK Parameter	Ratio of GLS Means (90% CI)		Compound Ratio
	AGN Treatment B/A (n=11)	GW433908 Treatment D/C (n=15)	GW433908 Treatment D/C Ratio/ AGN Treatment B/A Ratio
$AUC_{\tau,ss}$ (µg•h/mL)	3.16 (2.83-3.53)	3.40 (3.09-3.75)	1.08 (0.93-1.24)
$C_{max,ss}$ (µg.h/mL)	1.27 (1.11-1.46)	1.51 (1.34-1.70)	1.19 (0.99-1.43)
$C_{\tau,ss}$ (µg/mL)	10.73 (7.82-14.73)	12.68 (9.67-16.64)	1.18 (0.78-1.79)

Treatment A = AGN 600 mg BID for 14 days.
Treatment B = AGN 600 mg BID + RTV 100 mg BID for 14 days.
Treatment C = GW433908 700 mg[a] BID for 14 days.
Treatment D = GW433908 700 mg[a] BID + RTV 100 mg BID for 14 days

a. Each GW433908 oral film-coated 700mg tablet is the molar equivalent of 600mg APV.

SAFETY RESULTS: No serious adverse events or deaths were reported during this study. Twenty-seven of 32 subjects (84%) reported drug-related AEs while receiving either GW433908 or AGN-containing treatments. Overall, there appeared to be more drug- related AEs reported with AGN alone (92%), followed by AGN/RTV (87%), GW433908/RTV (63%), and GW433908 (53%).

CONCLUSIONS AND DISCUSSION: The study design is acceptable. Co-administration of RTV 100mg BID with AGN 600mg BID for 14 days increased steady-state plasma APV Cmax by approximately 27%; plasma APV AUC and C_{trough} were increased to values 3.2-fold and 10.7-fold, respectively, compared to those observed on administration of AGN 600mg BID without RTV. Co-administration of RTV 100mg BID with GW433908 700mg BID for 14-days increased steady-state plasma APV Cmax by approximately 51%; plasma APV AUC and C_{trough} were increased to values 3.4-fold and 12.7-fold, respectively, compared to those observed on administration of GW433908 700mg BID without RTV. Thus, plasma APV PK parameters were increased to a similar extent when either GW433908 or AGN was coadministered with RTV.

These data support the application of AGN drug-drug interaction data to the Lexiva label.

APV20001

TITLE: A Randomized, Multicenter, Partially Double-Blinded, Repeat Dose, Cross-Over Study to Assess the Safety, Tolerability, Pharmacokinetics, and Antiviral Effect of Two Doses of GW433908 Compared With AGENERASE (1200mg BID) when Given for 28 Days to Subjects Infected With HIV-1

BACKGROUND: APV20001 evaluated the safety, early antiviral effect and pharmacokinetics of two doses of GW433908 (1395mg and 1860mg) when administered in combination with abacavir (ZIAGEN, ABC) 300mg BID and lamivudine (EPIVIR, 3TC) 150mg BID for 28 days, compared to AGENERASE capsules (1200mg BID) in combination with ABC 300mg BID and 3TC 150mg BID.

OBJECTIVES: The primary objectives of the study were to compare the pharmacokinetic parameters of APV following repeat dosing of GW433908 and AGENERASE capsules (in the presence of ABC/3TC); to

compare the PK parameters of APV following repeat dosing of AGENERASE capsules alone and in combination with low dose ritonavir (NORVIR, RTV) (all in the presence of ABC/3TC); to assess the safety and tolerability of two doses of GW433908 when given as a component of combination therapy BID for 28 days to HIV infected subjects; and to assess the early antiviral effect of GW433908, as determined by changes from baseline in plasma HIV-1 ribonucleic acid (RNA) and helper-inducer T-lymphocyte surface antigen (CD4+) cell count, when given as a component of combination therapy BID for 28 days.

SUBJECTS AND STUDY DESIGN:

This was a partially double-blinded, randomized, repeat dose, cross-over study in HIV-infected subjects who had received ≤4 weeks of previous NRTI or non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment and no prior protease inhibitor (PI) treatment. Seventy-eight subjects were randomized and received study treatment in one of the following four treatment arms:

Treatment Arms for APV20001

		RANDOMIZED PHASE		OPEN-LABEL PHASE
Treatment Arm	**Planned Sample Size**	**Treatment Period 1 Days 1-28[a]**	**Treatment Period 2 Days 29-42[a]**	**Treatment Period 3 Day 43 – Week 48[a] OPTIONAL PERIOD**
1	28	GW433908, 1395mg[b] BID	**AGENERASE** capsules, 1200mg BID	**AGENERASE** capsules, 1200mg BID or **AGENERASE** capsules, 1200mg QD with 200mg RTV QD or **AGENERASE** capsules, 600mg BID with 100mg RTV BID
2	14	**AGENERASE** capsules, 1200mg BID	GW433908, 1395mg[b] BID	
3	28	GW433908, 1860mg[b] BID	**AGENERASE** capsules, 1200mg BID	
4	14	**AGENERASE** capsules, 1200mg BID	GW433908, 1860mg[b] BID	

a In combination with ABC (300mg BID) + 3TC (150mg BID)

b One GW433908 465mg tablet contains 400mg APV molar equivalents. The 1395mg dose of GW433908 contains 1200mg APV molar equivalents. The 1860mg dose of GW433908 contains 1600mg APV molar equivalents.

Summary of Demographics for APV20001
ITT (Exposed) Population; Randomized Phase

	GW433908		Total AGN (N=23)	Total (N=78)
	1395mg (N=26)	1860mg (N=29)		
Age (years)				
Median	35.0	36.0	32.0[a]	34.5
(Min, Max)	(21, 51)	(22, 54)	(21, 58)	(21, 58)
Sex (n, %)				
Female	9 (35)	9 (31)	7 (30)	25 (32)
Male	17 (65)	20 (69)	16 (70)	53 (68)
Race (n, %)				
White	16 (62)	20 (69)	11 (48)	47 (60)
Black	8 (31)	8 (28)	9 (39)	25 (32)
Asian	0	0	1 (4)	1 (1)
Other	2 (8)	1 (3)	2 (9)	5 (6)
Median Weight, kg	70.0	72.3	65.0[a]	70.0
(Min, Max)	(46, 118)	(52, 105)	(50, 99)	(46, 118)

PK sampling occurred on Days 1, 28 and 42. Subjects fasted for 8 h prior to and 3 h after administration of the first dose of study drug on Days 1, 28, and 42.

INVESTIGATOR AND STUDY LOCATION: There were 20 investigators for this study.

FORMULATION: GW433908, 465 mg tablets (batch number A99B22), AGENERASE, 150mg capsules.

SAMPLE COLLECTION: Fifteen serial whole blood samples for analysis of plasma GW433908 and/or APV concentrations were collected (PK sampling) over 24-h on Day 1. Serial whole blood samples were collected over 12-h on each of Days 28, 42 and 2 weeks after initiating an AGENERASE/RTV combination regimen.

Pharmacokinetic Sampling Schedule

	Planned Time Relative to Dosing (h)
Pre-dose	0
Post-dose	0.25
	0.5
	0.75
	1
	1.5
	2
	2.5
	3
	4
	6
	8
	10
	12
	24[a]

a. Collect 24-h sample on Day 1 only.

ASSAY: Plasma PK samples were analyzed for APV and GW433908 by GlaxoSmithKline International Bioanalysis BioMet, Research Triangle Park, NC, USA using a validated

method [redacted] The quality control samples had coefficients of variation less than or equal to [redacted], respectively for GW443908 and APV.

PHARMACOKINETIC DATA ANALYSIS: Non-compartmental methods by a validated pharmacokinetic analysis program were used. Summary statistics of pharmacokinetic parameters such as geometric means and coefficients of variation for Cmax,ss, tmax,ss, $C_{\tau,ss}$ and $AUC_{\tau,ss}$ were provided for each group. The geometric mean ratios with 90% confidence intervals were calculated between groups.

PHARMACOKINETIC RESULTS:

Table 1. Plasma APV PK Parameter Estimates in APV20001
Geometric Mean (95% CI)

Single Dose (Day 1)			
Plasma APV PK Parameter	**GW433908 1395mg (N=15)**	**GW433908 1860mg (N=22)**	**AGN 1200mg (N=16)**
AUC_{∞} (µg.h/mL)[a]	22.8 (18.7-27.8)	42.3 (34.1-52.5)	24.6 (18.9-32.0)
C_{max} (µg/mL)	4.64 (3.37-6.38)	7.94 (6.55-9.62)	7.19 (5.94-8.72)
t_{max} (h)[b]	2.5 (1.5-4.0)	2.0 (0.5-4.3)	1.3 (0.5-3.0)
$t_{1/2}$ (h)[a]	7.7 (5.9-10)	7.9 (6.2-10)	9.6 (6.5-14)
Steady-state (Days 28 and 42)			
Plasma APV PK Parameter	**GW433908 1395mg BID (N=22)**	**GW433908 1860mg BID (N=31)**	**AGN1200mg BID (N=53)**
$AUC_{\tau,ss}$ (µg.h/mL)	16.5 (13.8-19.6)	17.0 (14.9-19.5)	16.2 (14.3-18.3)
$C_{max,ss}$ (µg/mL)	4.82 (4.06-5.72)	4.78 (4.14-5.53)	6.80 (5.90-7.84)
$t_{max,ss}$ (h)[b]	1.3 (0.8-4.0)	1.5 (0.8-4.1)	1.0 (0.5-2.5)
$C_{\tau,ss}$ (µg/mL)	0.35 (0.27-0.46)	0.35 (0.27-0.45)	0.26 (0.21-0.31)

a. GW433908 1395mg N=15, GW433908 1860mg N=18, AGN N=16 for AUC_{∞} and $t_{1/2}$
b. t_{max} and $t_{max,ss}$ data presented as median (range)

Table 2. Plasma GW433908 PK Parameter Estimates in APV20001
Geometric Mean (95% CI)

Single Dose (Day 1)		
Plasma GW433908 PK Parameter	**GW433908 1395mg (N=10)**	**GW433908 1860mg (N=19)**
AUC_{last} (µg.h/mL)	0.008 (0.003-0.023)	0.017 (0.009-0.029)
C_{max} (µg/mL)	0.012 (0.007-0.021)	0.021 (0.014-0.032)
t_{max} (h)[a]	1.0 (0.50-3.0)	1.0 (0.50-3.0)
Steady-state (Days 28 & 42)		
Plasma GW433908 PK Parameter	**GW433908 1395mg BID (N=14)**	**GW433908 1860mg BID (N=25)**
$AUC_{last,ss}$ (µg.h/mL)	0.021 (0.011-0.039)	0.018 (0.010-0.032)
$C_{max,ss}$ (µg/mL)	0.020 (0.013-0.029)	0.021 (0.014-0.030)
$t_{max,ss}$ (h)[a]	1.0 (0.25-3.0)	1.0 (0.25-4.0)

a. t_{max} and $t_{max,ss}$ data presented as median (range)

Table 3. Steady-State Plasma APV PK Treatment Comparisons in APV20001
GLS Mean Ratio (90% CI)

Plasma APV PK Parameter	**GW433908 1395mg BID/ AGN 1200mg BID N=22**	**GW433908 1860mg BID/ AGN 1200mg BID N=31**
$AUC_{\tau,ss}$ (µg.h/mL)	0.96 (0.85-1.09)	1.07 (0.96-1.19)
$C_{max,ss}$ (µg/mL)	0.70 (0.59-0.82)	0.73 (0.63-0.85)
$C_{\tau,ss}$ (µg/mL)	1.28 (1.06-1.54)	1.46 (1.24-1.72)
$t_{max,ss}$ (h)[a]	1.39 (1.08-1.70)	1.75 (1.46-2.03)

a. LS mean ratio (90% CI) for $t_{max,ss}$

Table 4. Plasma APV PK Comparison in APV20001
Steady State/Single Dose (GLS Mean Ratio (90% CI))

	GW433908		**AGN 1200mg BID (N=16)**
Plasma APV PK Parameter	**1395mg BID (N=15)**	**1860mg BID (N=18)[a]**	
$AUC_{\tau,ss}/AUC_{\infty}$	0.73 (0.61-0.87)	0.55 (0.47-0.66)	0.77 (0.65-0.91)

a. Plasma APV AUC_{∞} could not be estimated for 4 subjects (Subjects 127, 159, 194, and 275) receiving GW433908 1860mg.

Figure 1. Effect of AAG on APV AUCτ,ss on Day 28

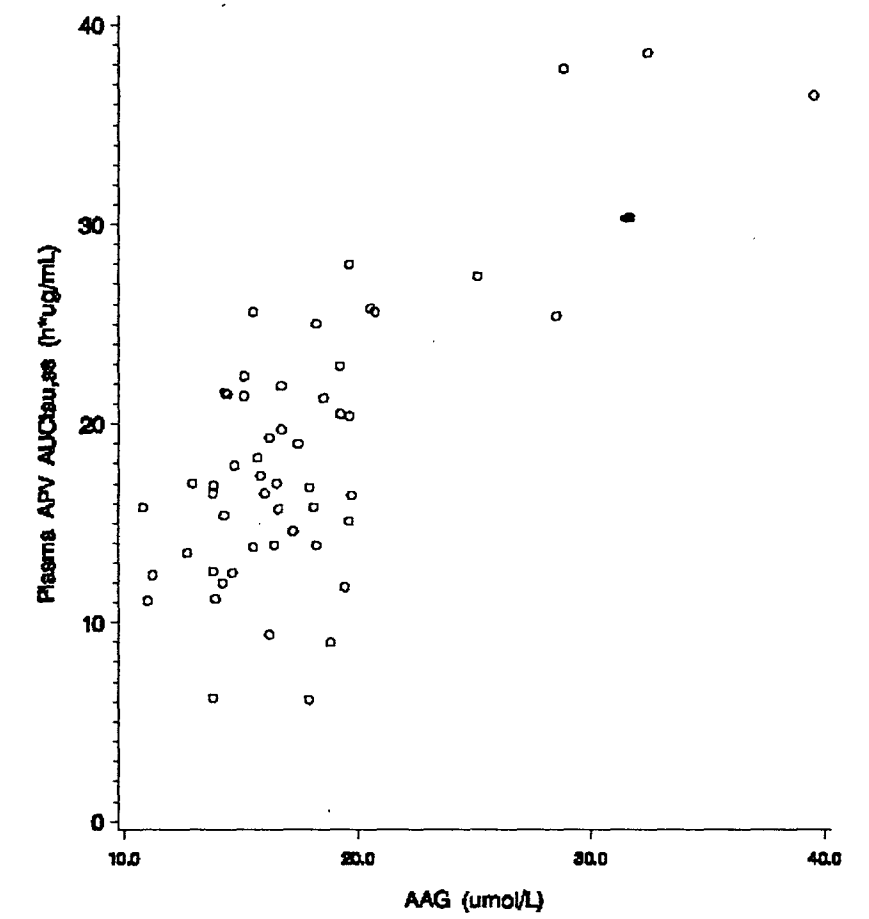


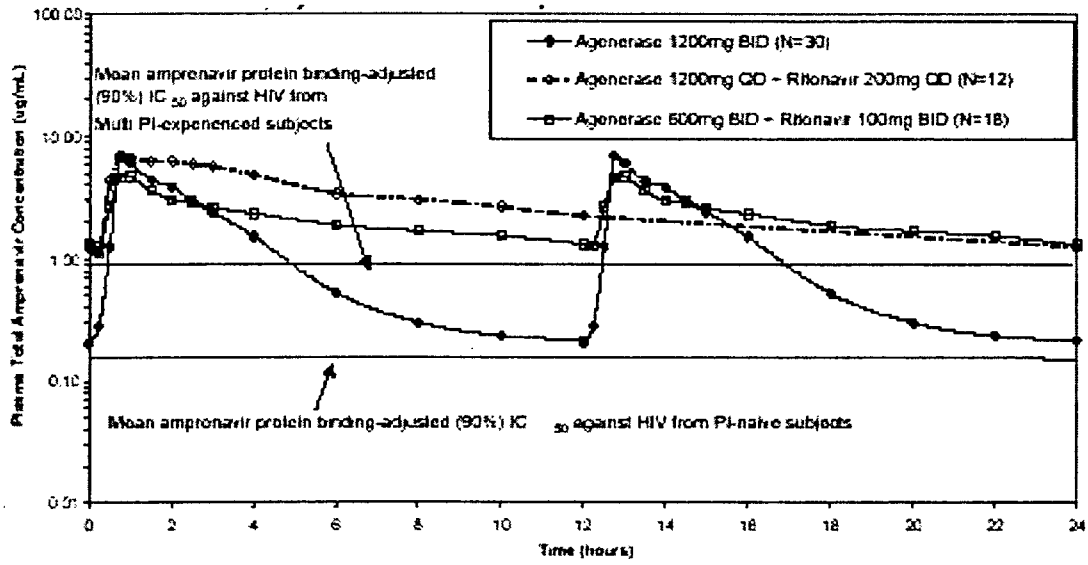
Table 5. Plasma APV Pharmacokinetic Parameter Estimates with and without concomitant RTV Geometric Mean (95% CI)

Plasma APV PK Parameter	AGN 600mg BID + RTV 100mg BID N=18[a]	AGN 1200mg QD + RTV 200mg QD N=12	AGN 1200mg BID N=30
$AUC_{\tau,ss}$ (µg.h/mL)[b]	28.4 (21.8-36.9)	68.2 (60.0-77.7)	17.0 (14.2-20.3)
$C_{max,ss}$ (µg/mL)	5.16 (4.07-6.53)	7.75 (6.95-8.65)	6.85 (5.63-8.32)
$C_{\tau,ss}$ (µg/mL)[b]	1.51 (1.15-2.00)	1.40 (1.10-1.78)	0.25 (0.19-0.33)

a One subject received AGN 600mg BID + RTV 200mg BID: $AUC_{\tau,ss}$=24.5, $C_{max,ss}$= [illegible] and $C_{\tau,ss}$=1.78.
b τ = 12 hours for BID regimen and 24 hours for QD regimen.

BEST POSSIBLE COPY

Figure 2. Median Steady-State Plasma Total Amprenavir Concentration-Time Profiles



EFFICACY RESULTS: In subjects who had received ≤4 weeks of previous NRTI or NNRTI treatment and no prior PI treatment, an antiviral effect was observed through 28 days of treatment. The effect was maintained through 42 days of treatment, whether subjects started on GW433908 and then switched to AGENERASE, or started on AGENERASE and switched to GW433908. There were very few differences between the treatment arms, indicating that, in this study, GW433908 and AGENERASE have similar efficacy profiles.

Over 28 days, 42% and 45% of subjects receiving GW433908 1395mg and GW433908 1860mg, respectively, had a plasma HIV-1 RNA level <400 copies/mL. 39% of subjects in the combined AGENERASE treatment arms had a plasma HIV-1 RNA <400 copies/mL.

Over 28 days, 85% and 79% of subjects receiving GW433908 1395mg and GW433908 1860mg, respectively, had a 1.5 log10 copies/mL decrease in plasma HIV-1 RNA from baseline. 83% of subjects in the combined AGENERASE treatment arms had a 1.5 log10 copies/mL decrease in plasma HIV-1 RNA from baseline.

SAFETY RESULTS: The safety results demonstrated that the two doses of GW433908 studied (1365mg and 1860mg BID) were well tolerated in HIV-1 infected subjects over a 28-day period. No new safety concerns were raised in this study.

CONCLUSIONS:

- Both GW433908 1395mg BID and GW433908 1860mg BID delivered similar plasma APV AUCτ,ss values, lower Cmax,ss values (~30% lower), and higher Cτ,ss values (~28% higher for GW433908 1395mg BID and ~46% higher for GW433908 1860mg BID) as compared to AGENERASE 1200mg BID.
- GW433908 was rapidly converted to APV, with minimal GW433908 in plasma (<0.6% of corresponding APV AUC and <1.6% of corresponding APV Cmax,ss).
- Plasma APV AUC values decreased between Day 1 and Day 28 for all three treatments; however the percent decrease for the GW433908 1860mg treatment was greater (~23% for

AGENERASE 1200mg BID, ~26% for GW433908 1395mg, and ~46% for GW433908 1860mg BID).

- Plasma AAG concentrations were consistently correlated with plasma APV PK. Changes in plasma AAG concentrations and changes in plasma APV AUCτ,ss values over the first 28 days of the study were also significantly correlated.
- Coadministration of AGENERASE 600mg BID + RTV 100mg BID resulted in a 64% increase in plasma APV AUCτ,ss, a 6.1-fold increase in plasma APV Cτ,ss, and a 30% reduction in plasma APV Cmax,ss compared with AGENERASE 1200mg BID.
- Coadministration of AGENERASE 1200mg QD + RTV 200mg QD resulted in a 62% increase in plasma APV AUCτ,ss, a 4.2-fold increase in plasma APV Cτ,ss, and no change in plasma APV Cmax,ss compared with AGENERASE 1200mg BID.

APV30002

TITLE: A Randomized, Open-Label, Two Arm Trial to Compare the Safety and Antiviral Efficacy of GW433908/Ritonavir QD to Nelfinavir BID When Used in Combination with Abacavir and Lamivudine BID for 48 Weeks in Antiretroviral Therapy Naïve HIV-1 Infected Subjects

BACKGROUND: At the time this study (APV30002) was designed, limited efficacy and safety data were available for GW433908. The efficacy results from APV20001 demonstrated a potent and rapid antiviral effect (2 log10 copies/mL reduction in plasma HIV-1 RNA in each treatment group) in subjects who had received ≤4 weeks of treatment. The safety results from APV20001 demonstrated that the two doses of GW433908 studied (1395mg and 1860mg BID) were well-tolerated and that adverse events reported were generally mild to moderate in intensity and similar to those reported with AGENARASE. Nelfinavir (NFV, Viracept) is a marketed PI and is widely used as a first choice PI. When given as part of a combination antiviral treatment regimen, NFV has demonstrated rapid and prolonged reductions in plasma HIV-1 RNA levels and increased CD4+ counts. In this trial, NFV was chosen as the standard with which to compare the antiviral potency and safety of GW433908 in ART-naïve HIV-1 infected adults. In order to obtain long-term comparative data, this study (APV30002) compared the safety, antiviral efficacy and durability of GW433908 (1400mg QD)+RTV (200mg QD) to NFV (1250mg BID), both given in combination with ZIAGEN (abacavir, ABC) and EPIVIR (lamivudine, 3TC) BID.

OBJECTIVES: The primary objective was to compare the magnitude and durability of antiviral response of GW433908/RTV QD and NFV BID when used in combination with ABC/3TC BID over 48 weeks in ART-naïve subjects. One of the secondary objectives of the study was to confirm that steady-state plasma amprenavir trough concentrations obtained with GW433908 1400mg QD + RTV 200mg QD were similar to those predicted based on AGN 1200mg QD + RTV 200mg QD data.

SUBJECTS AND STUDY DESIGN: This was a randomized, open-label, two arm study in HIV-1 infected ART-naïve subjects (defined as fewer than 4 weeks of previous therapy with an NRTI and no previous exposure to any PI or NNRTI). The study was performed at study centers located in North America, Europe, Australia and South Africa. Six hundred forty-nine subjects were randomized in a 1:1 scheme to one of the following two treatment groups:

Group 1: GW433908 1400mg QD + RTV 200mg QD + ABC 300mg BID + 3TC 150mg BID (322 subjects)

Group 2: NFV 1250mg BID + ABC 300mg BID + 3TC 150mg BID (327 subjects)

The control group for this study consisted of those subjects randomized to Treatment Group 2, who received the active comparator. Randomization was stratified according to subject plasma HIV-1 RNA level at screening (1000-10,000 copies/mL; >10,000-100,000 copies/mL; or >100,000 copies/mL).

	908/RTV QD N=322	NFV BID N=327	Total N=649
Age (years)			
Median	36	36	36
Min, Max	18, 69	18, 68	18, 69
Sex, n (%)			
Female	96 (30)	78 (24)	174 (27)
Male	226 (70)	249 (76)	475 (73)
Race, n (%)			
White	163 (51)	178 (54)	341 (53)
Black	122 (38)	109 (33)	231 (36)
Asian	5 (2)	7 (2)	12 (2)
American Hispanic	24 (7)	25 (8)	49 (8)
Other	8 (2)	8 (2)	16 (2)
Median Weight, kg (range)	70 (38-132)	70 (39-165)	70 (38-165)
Median Height, cm (range)	173 (144-203)	173 (140-197)	173 (140-203)

INVESTIGATOR AND STUDY LOCATION: This was a multicenter study conducted by 101 investigators.

FORMULATION: GW433908, 465mg tablets (batch numbers E00B136, E00B173, E00B217, E01B115, E01B154, E01B259, E01B74, E01B81, E00B203, E00B4, E01B118, E01B47, E01B81 and E01B88), 700mg tablets (batch numbers B044089, B047964, E01B132, E01B79, B041065, B044089, E01B151 and E01B93); Novir (RTV) 100mg capsules; Viracept (NFV) 250mg tablets; Ziagen (ABC) 300mg tablets; Epivir (3TC) 150mg tablets.

SAMPLE COLLECTION: A total of 50 subjects assigned to the GW433908/RTV arm underwent trough pharmacokinetic sampling at the Week 4, 8, and 12 visits to assess steady-state plasma APV concentrations. Ten of these subjects underwent additional pharmacokinetic sampling and had samples drawn at trough (prior to dose), 2 hours and 4 hours post dose at the Week 4 visit.

ASSAY: Plasma PK samples were analyzed for APV concentrations by GlaxoSmithKline Worldwide Bioanalysis, Research Triangle Park, NC, USA, using a validated [redacted] method [redacted] The quality control samples had coefficients of variation less than or equal to [redacted] for APV.

PHARMACOKINETIC DATA ANALYSIS: Plasma APV $C_{\tau,ss}$ values were summarized by week and overall.

APPEARS THIS WAY
ON ORIGINAL

PHARMACOKINETIC RESULTS:

Table 1. Plasma APV Cτ,ss Values (µg/mL) in APV30002

Median (range)			
Week 4	**Week 8**	**Week 12**	**Overall**
All subjects with Plasma APV $C_{\tau,ss}$ Data			
(N=32)	(N=30)	(N=29)	(N=38)
1.73	0.978	0.995	1.43
Subjects with Plasma APV $C_{\tau,ss}$ Data at all Visits (N=22)			
1.11	0.902	0.988	1.25

BLQ = below the limit of quantitation

EFFICACY RESULTS: Please refer to Russ Fleischer's review.

SAFETY RESULTS: Please refer to Russ Fleischer's review.

CONCLUSIONS: The regimen of GW433908 1400mg QD + RTV 200mg QD delivered a median plasma APV Cτ,ss value of 1.43 µg/mL (n=38; range: µg/mL).). These observed values are similar to previously reported values (APV10009). The median IC_{50} value for APV against HIV was 0.015 µg/mL (n=38; range 0.003-0.124 µg/mL). The regimen of GW433908 1400mg QD + RTV 200mg QD delivered a median non-protein binding-adjusted plasma APV Cτ,ss/IC_{50} value of 73.1 (range: 18.3-966). Considering protein binding of 90% for APV, the median protein-binding adjusted plasma APV Cτ,ss/IC_{50} value achieved in this study was 7.31 (range: 1.83-96.6).

APV30003

TITLE: A Phase III, Randomized, Multicenter, Parallel Group, Open-Label, Three Arm Study to Compare the Efficacy and Safety of Two Dosing Regimens of GW433908/Ritonavir (700mg/100mg twice daily or 1400mg/200mg once daily) versus Lopinavir/Ritonavir (400mg/100mg twice daily) for 48 Weeks in Protease Inhibitor Experienced HIV-Infected Adults Experiencing Virological Failure

OBJECTIVES: The primary objective was to test the non-inferiority of two different dosage regimens of GW433908/RTV versus LPV/RTV (as measured by average area under the curve minus baseline (AAUCMB) in plasma HIV-1 RNA) at both 24 and 48 weeks, when each are administered in combination with two active reverse transcriptase inhibitors (RTIs), in an antiretroviral treatment-experienced population experiencing virological failure. One of secondary objectives was to characterize steady-state plasma APV and LPV trough concentrations.

SUBJECTS AND STUDY DESIGN: This was a randomized, parallel group, three-arm, open-label, multicenter, comparative study of two dosage regimens of GW433908/RTV versus LPV/RTV in combination with two active RTIs, performed in North and South America, Europe, and Australia. Subjects were PI-experienced with at least 12 consecutive weeks of prior PI experience. Three hundred twenty (320) subjects were randomized, in a 1:1:1 ratio, to the following treatment groups:

Group 1: GW433908 700mg BID + RTV 100mg BID + two active RTIs (107 subjects)

Group 2: GW433908 1400mg QD + RTV 200mg QD + two active RTIs (107 subjects)

Group 3: LPV/RTV 400mg/100mg BID + two active RTIs (106 subjects)

Randomization was stratified according to subject plasma HIV-1 RNA level at screening (1000-10,000 copies/mL; >10,000-100,000 copies/mL; >100,000 copies/mL).

	908/RTV QD N=105	908/RTV BID N=107	LPV/RTV BID N=103	Total N=315
Age (years)				
Median	41	39	41	40
Min, Max	24, 58	24, 71	29, 69	24, 71
Sex, n (%)				
Female	17 (16)	14 (13)	17 (17)	48 (15)
Male	88 (84)	93 (87)	86 (83)	267 (85)
Race, n (%)				
White	77 (73)	75 (70)	59 (57)	211 (67)
Black	20 (19)	22 (21)	33 (32)	75 (24)
Asian	1 (<1)	1 (<1)	0	2 (<1)
American Hispanic	7 (7)	9 (8)	11 (11)	27 (9)
Median Weight, kg (range)	72 (46-119)	74 (50-128)	75 (46-119)	74 (46-128)
Median Height, cm (range)	175 (145-196)	175 (155-198)	175 (152-200)	175 (145-200)

INVESTIGATOR AND STUDY LOCATION: This was a multicenter study conducted by 103 investigators.

FORMULATION: GW433908, 700mg tablets (batch numbers B041065, B048577, B044089, B059742, B060071, B060988, E00B149, E00B223, E01B79, and E01B212); Novir (RTV) 100mg capsules; Kaletra (LPV/RTV) capsules, 133.3mg/33.3mg; Viread (TDF), 300mg tablets.

SAMPLE COLLECTION: Plasma samples for measurement of APV or LPV trough concentrations were collected from all subjects enrolled in the study at Weeks 4, 8, 12 and 48. PK samples were collected within 10-14 hours (for subjects receiving a BID regimen), or 22-26 hours (for subjects receiving a QD regimen) following a dose of study drug.

ASSAY: Plasma PK samples were analyzed for GW433908 and APV by [redacted] using a [redacted] method. Plasma PK samples were analyzed for LPV by [redacted] using a validated [redacted] method. The quality control samples had coefficients of variation less than or equal to [redacted] for APV.

PHARMACOKINETIC DATA ANALYSIS: Plasma APV and LPV $C_{\tau,ss}$ values were summarized by week and overall.

PHARMACOKINETIC RESULTS:

Table 1. Summary of Plasma APV Cτ,ss Values (μg/mL) in APV30003

Evaluations		908/RTV QD		908/RTV BID	
		All Data	Subjects with Data at All Visits	All Data	Subjects with Data at All Visits
Week 4		(N=37)	(N=16)	(N=66)	(N=26)
	Median (range)	1.41	1.39	1.86	1.86
	GeoMean (95% CI)	1.28 (1.02-1.61)	1.25 (0.848-1.84)	1.62 (1.42-1.85)	1.63 (1.34-1.99)
Week 8		(N=39)	(N=16)	(N=69)	(N=26)
	Median (range)	1.32	1.49	1.55	1.51
	GeoMean (95% CI)	1.40 (1.09-1.80)	1.60 (1.09-2.36)	1.50 (1.26-1.78)	1.46 (1.12-1.91)
Week 12		(N=47)	(N=16)	(N=61)	(N=26)
	Median (range)	1.17	1.25	1.82	1.77
	GeoMean (95% CI)	1.15 (0.937-1.42)	1.15 (0.816-1.63)	1.76 (1.54-2.01)	1.71 (1.43-2.06)
Week 48		(N=44)	(N=16)	(N=48)	(N=26)
	Median (range)	1.05	1.03	1.64	1.61
	GeoMean (95% CI)	1.12 (0.924-1.37)	0.917 (0.631-1.33)	1.64 (1.39-1.93)	1.43 (1.15-1.78)
Overall[1]		(N=70)	(N=16)	(N=84)	(N=26)
	Median (range)	1.37	1.54	1.71	1.64
	GeoMean (95% CI)	1.40 (1.22-1.60)	1.35 (0.991-1.83)	1.74 (1.56-1.93)	1.63 (1.37-1.93)

BLQ = below the limit of quantification

1. Overall includes summary of individual average values

Table 2. Summary of Plasma LPV Cτ,ss Values (μg/mL) in APV30003

Evaluations		LPV/RTV BID	
		All Data	Subjects with Data at All Visits
Week 4		(N=52)	(N=25)
	Median (range)	6.54	5.49
	GeoMean (95% CI)	5.75 (4.78-6.93)	5.48 (4.20-7.15)
Week 8		(N=54)	(N=25)
	Median (range)	6.72	6.54
	GeoMean (95% CI)	6.34 (5.54-7.27)	6.16 (4.88-7.78)
Week 12		(N=59)	(N=25)
	Median (range)	6.37	5.67
	GeoMean (95% CI)	5.95	5.53
Week 48		(N=56)	(N=25)
	Median (range)	5.86	6.12
	GeoMean (95% CI)	5.47 (4.55-6.57)	5.67 (4.17-7.71)
Overall[1]		(N=81)	(N=25)
	Median (range)	6.06	5.78
	GeoMean (95% CI)	6.01 (5.36-6.73)	6.09 (4.91-7.56)

BLQ = below the limit of quantitation

1. Overall includes summary of individual values

Table 3. Summary of Plasma APV and LPV Cτ,ss/Baseline IC50 in APV30003[1]

	908/RTV QD (N=70)	908/RTV BID (N=81)[2]	LPV/RTV BID (N=76)[3]
$C_{\tau,ss}$ (µg/mL)	1.37	1.71	6.06
Baseline IC_{50} (µg/mL)	0.008 (0.001-0.048)	0.008 (0.001-0.144)	0.003 (0.001-0.146)
$C_{\tau,ss}$/Baseline IC_{50}	193.4 (BLQ-1172)	217.3 (11.9-2403)	1681 (BLQ-9250)
$C_{\tau,ss}$/Baseline IC_{50} adjusted for protein binding[4]	19.3 (BLQ-117.2)	21.7 (1.19-240.3)	16.8 (BLQ-92.5)

BLQ = below the limit of quantitation ([redacted] for APV and [redacted] for LPV)

1. Data presented as median (range)
2. N=84 for $C_{\tau,ss}$ for 908/RTV BID
3. N=81 for $C_{\tau,ss}$ for LPV/RTV BID
4. Protein binding of 90% applied to APV and 99% applied to LPV

Similar plasma APV Cτ,ss values were observed for subjects receiving, versus not receiving, concurrent TDF. The geometric mean (95% CI) plasma APV Cτ,ss value for the 908/RTV QD regimen with TDF was 1.37 µg/mL (1.18 - 1.60 µg/mL) versus without TDF was 1.43 µg/mL (1.10 - 1.86 µg/mL). The geometric mean (95% CI) plasma APV Cτ,ss value for the 908/RTV BID regimen with TDF was 1.76 µg/L (1.56-1.98 µg/mL) versus without TDF was 1.69 µg/mL (1.35-2.1µg/mL).

EFFICACY RESULTS: Please refer to Russ Fleischer's review.

SAFETY RESULTS: Please refer to Russ Fleischer's review.

CONCLUSIONS: The geometric mean plasma APV Cτ,ss (908/RTV QD: 1.40 µg/mL; 908/RTV BID: 1.74 µg/mL) and LPV Cτ,ss (6.01 µg/mL) values observed in this study are similar to previously reported values. Geometric mean (95% CI) plasma APV Cτ,ss values achieved for the 908/RTV BID regimen, 1.74 µg/mL (1.56-1.93 µg/mL), were higher than for the 908/RTV QD regimen, 1.40 µg/mL (1.22-1.60 µg/mL).

RD2002/00142/00

TITLE: Mechanism of Hydrolysis of GW433908A to Amprenavir *in vitro* with Intestinal Alkaline Phospatase and Intestinal Brush Border Membrane Vesicles

OBJECTIVES: The enzymatic conversion of GW433908A (di-sodium salt) to amprenavir was investigated with two *in vitro* assays, isolated intestinal alkaline phosphatase and intestinal brush border membrane vesicles (BBMV), to better understand the mechanism of hydrolysis of GW433908 after oral administration.

METHODS:

Rat and dog alkaline phosphatase (AP) studies:

Brush border membrane vesicle (BBMV) studies:

RESULTS:

Rat and dog alkaline phosphatase (AP) studies:

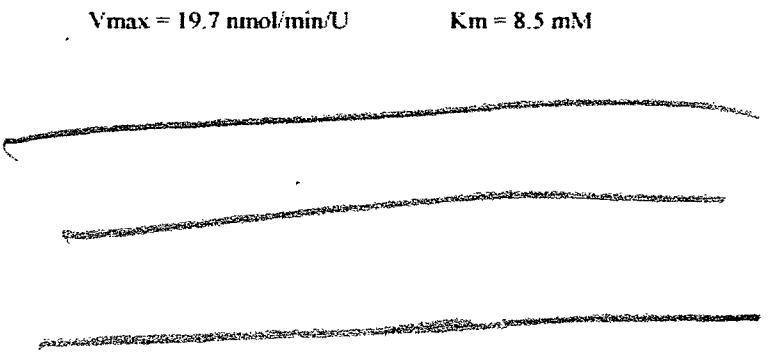
Reactions were concentration-dependent and saturable in the range of GW433908A for rat and dog intestinal alkaline phosphatase, respectively. Estimates of Vmax and Km were 19.7 nmol/min/U and 8.5 mM with isolated rat intestinal alkaline phosphatase, and 11.6 nmol/min/U (38.3 nmol/min/mg) and 4.5 mM with isolated dog intestinal alkaline phosphatase, respectively.

Figure 1 Conversion of GW433908A to Amprenavir by Dog Intestinal Alkaline Phosphatase

V_{max} = 11.6 nmol/min/U K_m = 4.5 mM

APPEARS THIS WAY
ON ORIGINAL

Figure 2 Conversion of GW433908A to Amprenavir by Rat Intestinal Alkaline Phosphatase



Brush border membrane vesicle (BBMV) studies:

Results show that BBMV catalyzed the conversion of GW433908A to amprenavir at pH 10.2, and generally correlated with known expression of alkaline phosphatase (duodenum>jejunum>ileum) in the intestinal tract. Reactions were generally concentration-dependent and saturable in the range of 0.5 to 10 mM GW433908A.

Table 1. Estimates of Km and Vmax for Brush Border Membrane Vesicle-Catalyzed Conversion of GW433908A to Amprenavir

Species	Intestinal Segment	K_m (mM)	V_{max} (nmol/mg/20 min)
Rat	Duodenum	3.8 ± 3.0	113 ± 37
	Jejunum	3.4 ± 0.9	102 ± 10
	Ileum	13 ± 35	42 ± 73
Dog	Duodenum	2.4 ± 0.4	1743 ± 89
	Jejunum	0.6 ± 0.4	776 ± 104
	Ileum	0.9 ± 0.4	886 ± 101
Human	Duodenum	1.2 ± 0.9	68 ± 13
	Jejunum	0.2 ± 0.1	154 ± 7.0
	Ileum	0.5 ± 0.1	104 ± 5.0

Evidence from other Studies: In Study 02ARS0078 (In vitro permeability of GW433908A across Caco-2 cells monolayers, Report No. RD2002/00489/00), intracellular transport of GW433908, and conversion of GW433908 to APV, was examined with the Caco-2 intestinal layer model system. When GW433908A was placed on the apical side of the cell monolayer, APV accounted for 99% of the material transported

to the basolateral side. No significant concentrations of GW433908X were found on the basolateral side. Some GW433908A was hydrolysed to APV over time on the apical side. These data suggested that GW433908A was hydrolysed at or near the intestinal membrane and that only APV was absorbed to any significant extent.

In another Study 98APK0135 (Pharmacokinetic study after oral administration of GW433908G to portal vein-cannulated Han Wistar rats and a Beagle dog, Report No. RD1998/02935/01), portal vein-cannulated rats and a portal vein cannulated dog were administered GW433908G orally (112 mg/kg and 35 mg/kg, respectively), blood samples taken from the portal vein and plasma analyzed for 908 andAPV. Estimates of systemic exposure (AUC) to 908 and APV indicated that less than 1% of the prodrug was intact in the portal vein in either species, and individual concentration ratios of 908 to APV were no more than 2.5%. These data corroborated the hypothesis that 908 is primarily hydrolyzed to APV at or near the intestinal membrane and not absorbed to a great extent.

CONCLUSIONS: These studies suggest that conversion of GW433908A to amprenavir was concentration-dependent and saturable and confirm that intestinal alkaline phosphatase can convert GW433908A to amprenavir. Study 98APK0135 further indicateds that GW433908 primarily converted to APV at or in the apical endothelium of the intestinal membrane.

COMMENT TO THE SPONSOR: Has any similar study been conducted with human alkaline phosphatase since this piece of information will provide direct evidence of alkaline phosphatase involvement in the conversion of fosamprenavir to APV in humans?

Dissolution Data

TITLE: Dissolution Data for fosamprenavir 700 mg Tablets

BACKGROUND: The proposed dissolution method below is acceptable (It was reviewed by Dr. Jennifer DiGiacinto prior to the NDA submission, IND 58,627 (SN#0050)). However, this dissolution method is not able to discriminate tablet variants B and C from tablet variant A. Study APV 10015 demonstrated that tablet variants B and C delivered 13-16% lower plasma APV exposure and were not bioequivalent to tablet variant A.

The sponsor further developed a [redacted] dissolution test to supplement the above-mentioned dissolution test. This test is intended to discriminate tablet variant A from tablet variants B and C. During development of the [redacted] dissolution method, physical properties of the drug substance such as pH solubility profile and pKa values were considered to achieve optimum discrimination among tablet variants. The [redacted] dissolution method development utilized the work conducted on the sponsor's in house [redacted] model that demonstrated good correlation with results from bioequivalence study APV10015 yielding the same rank order (A>B>C) that was observed in vivo. In the sponsor's current plan, the proposed [redacted] test described will be conducted initially on [redacted] commercial batches at release. If the data on these [redacted] batches provide the assurance of product consistency required, then it is proposed to discontinue the application of this test as a regulatory specification. The traditional dissolution test will continue to be used as a routine quality control test.

METHODS:

1. The proposed dissolution method for fosamprenavir 700 mg tablet is as follows:

Apparatus	USP II (paddle) with a volume of [redacted]
Rotation Speed	[redacted]
Temperature	37.5°C

Medium	[redacted]
Sampling Time	30-minute
Analytical Method	[redacted]

The proposed dissolution specification for fosamprenavir 700 mg tablet is Q = [redacted] dissolved in 30 minutes. The original proposal was at [redacted]-minute timepoint. The sponsor voluntarily tightened the specification based on their dissolution test results and the failed BE study.

2. The proposed [redacted] dissolution method for fosamprenavir 700 mg tablet is as follows:

Apparatus	USP II (paddle) with a volume of [redacted]
Rotation Speed	50 rpm
Temperature	37.5°C
Medium 1	[redacted]
Medium 2	[redacted]
Sampling Time	[redacted]
Analytical Method	[redacted]

The proposed dissolution specification for fosamprenavir 700 mg tablet is Q ≥ [redacted], dissolved in [redacted], (mean (n=24)% label claim released).

The acceptance criterion of mean release from [redacted] tablets of not less than [redacted], of label claim at the [redacted] timepoint is based on the batch data presented in Appendix (Tables 6-12). The rationale for this acceptance criterion is based on:

- The sample size of [redacted] tablets was selected due to the high individual tablet variability seen with the [redacted] test.
- The [redacted] timepoint provided for the best discrimination between sample populations of the tablet variant A batches from tablet variant B and C batches without increasing variability to an unacceptably high level.
- This test requires that all batches show greater release than the mean value (n = 24) recorded for tablet variants B (Batch B037578) and C (Batch B050889) used in APV10015.

APPEARS THIS WAY
ON ORIGINAL

RESULTS:

1. Traditional dissolution data:

Figure 1. Mean Dissolution Profiles for Fosamprenavir Tablet Batches used in Biostudies APV10006 and APV10015

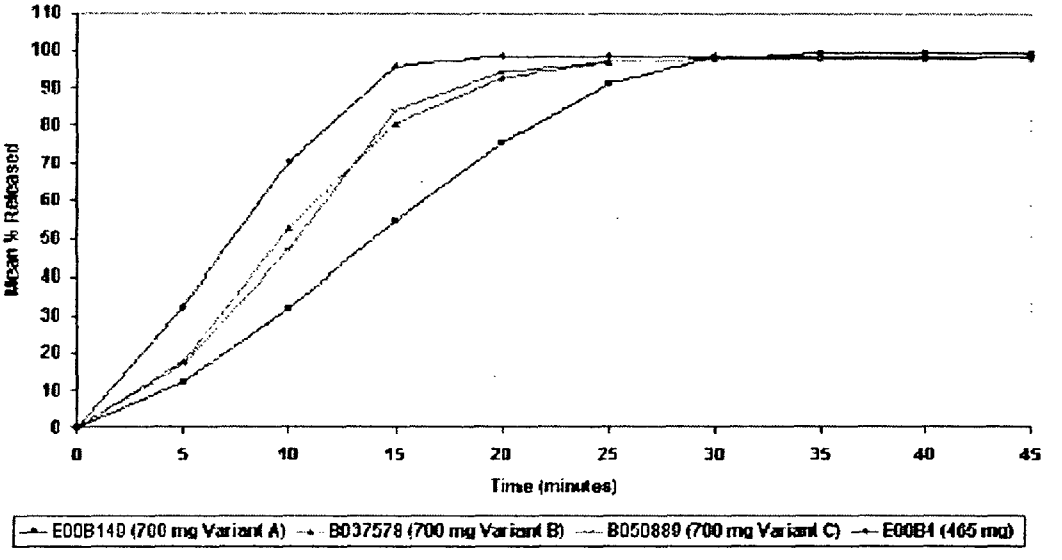
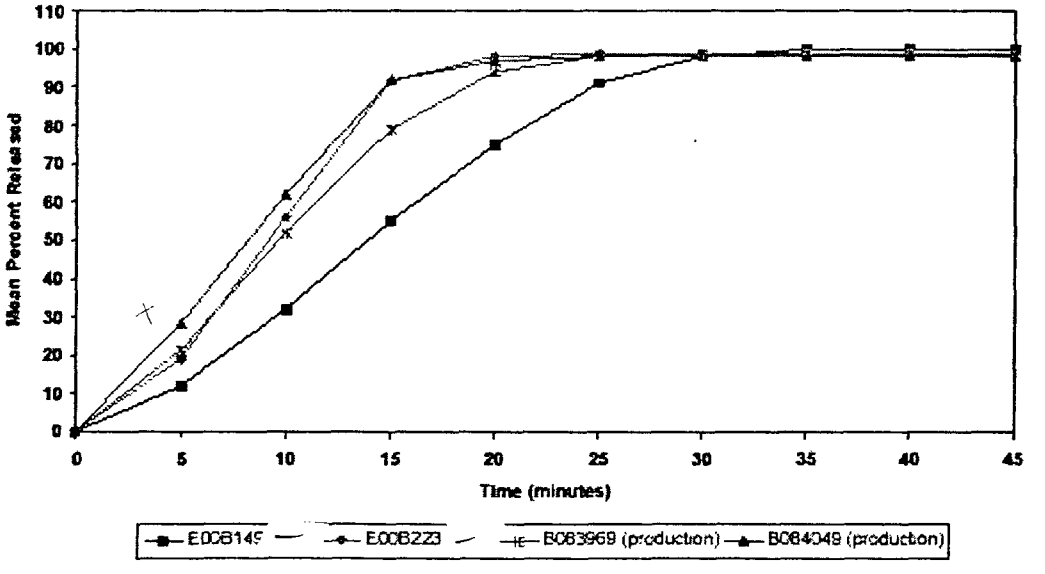


Figure 2. Mean Dissolution Profiles for Batches of Variant A Fosamprenavir Tablets, 700 mg



2. Bio-predictive dissolution data:

Figure 3. Comparison of Mean Dissolution Profiles (n = 24) for Fosamprenavir Tablets, 700 mg Variant A, B and C Batches used in APV10015 and APV10021 using the — Dissolution Test

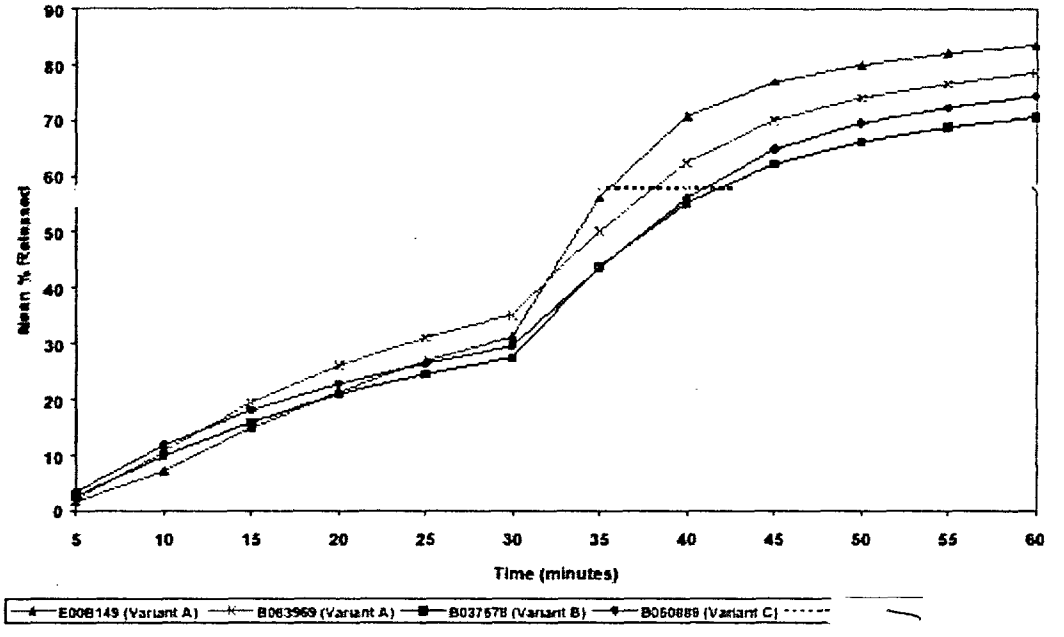


Figure 4. Comparison of Mean Dissolution Profiles (n = 24) for Fosamprenavir Tablets (Variant A), 700 mg Manufactured According to the Proposed Commercial Process using the — — Dissolution Test

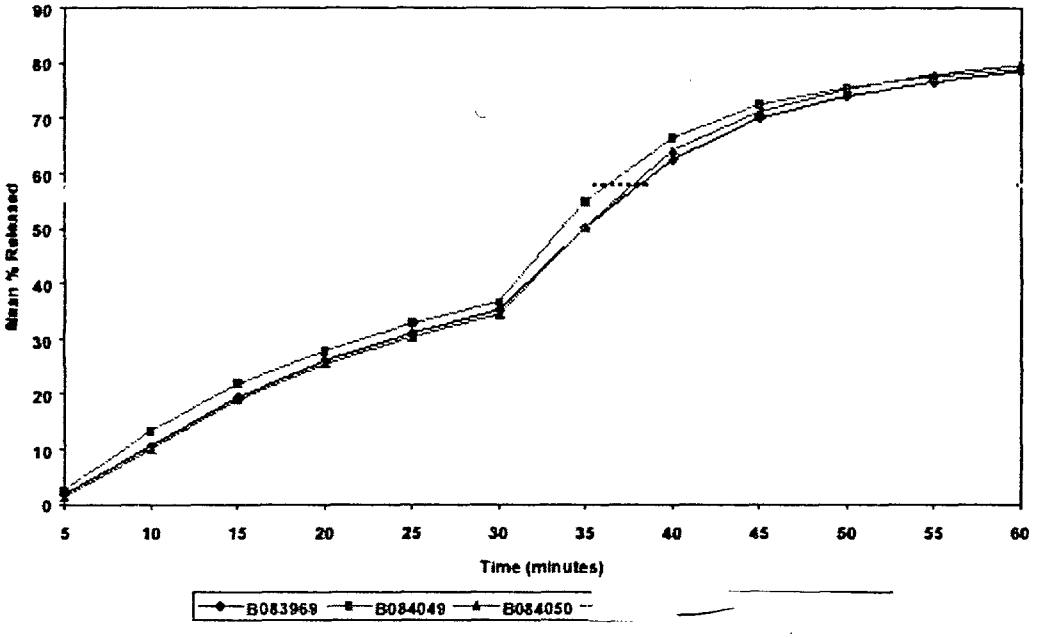
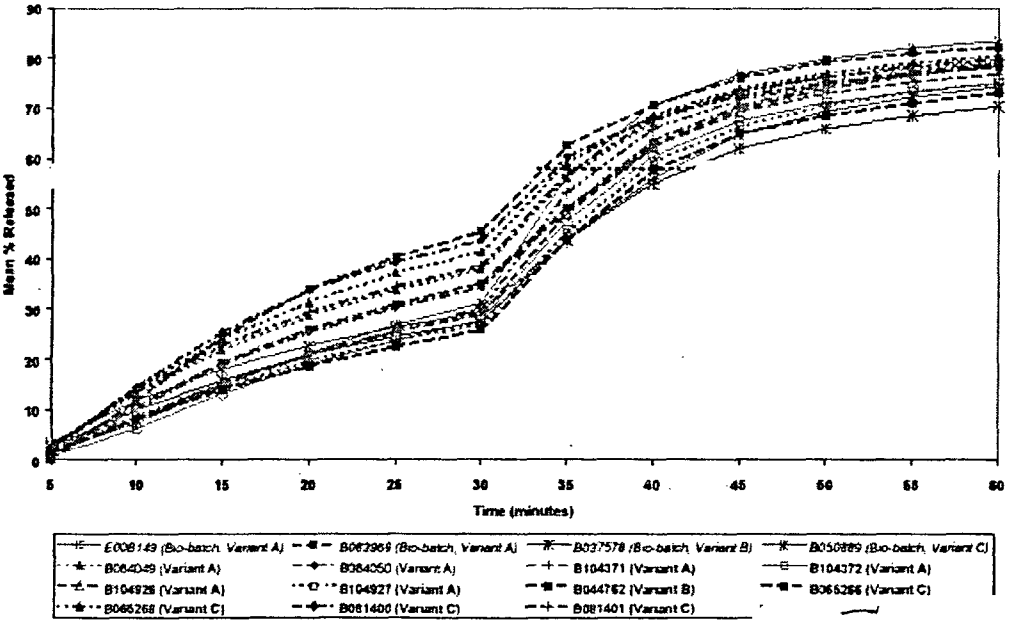


Figure 5. Comparison of Mean Dissolution Profiles (n = 24) for Additional 700 mg Fosamprenavir Tablets (Variants A, B and C) using the — Dissolution Test



CONCLUSIONS AND DISCUSSION: The traditional dissolution results comply well with the proposed specification using the proposed dissolution method and are acceptable.

The [redacted] appeared to discriminate between tablet variant A (Batch E00B149) and tablet variants B (Batch B037578) and C (Batch B050889) used in the study APV10015. Batches of tablet variant A (Batches E00B149 and B083969, a proposed commercial batch) passed the proposed specification of [redacted] dissolution test, while tablet variant B and variant C failed to meet the proposed specification (Figure 3). These results are consistent with the results observed in bioequivalence studies APV10015 and APV10021 (Figure 4).

The additional data for the [redacted], dissolution method provided in the Amendment of August 1st, 2003 demonstrated that, although all batches of tablets made from variant A drug substance passed the test, batches of tablets made from variant B (1) and variant C (4) drug substance also passed the test (Figure 5). Thus the test does not appear to be discriminatory. It is not clear that these batches of tablet variants B and C will be bioequivalent to tablet variant A.

COMMENT TO THE SPONSOR: Based on these data, it is insufficient to conclude that this dissolution method will assure the *in vivo* performance.

APPENDIX:

Table 1. Dissolution Results for Fosamprenavir Tablets, 465 mg used in Study APV10006

Batch No. and Variant (Scale)	% Fosamprenavir Released														
[redacted] (A)	Tablet Number														
Time (Min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	Min	Max
5	[redacted]												32		
10													70		
15													96		
20													99		
25													99		
30													99		
35													99		
40													99		
45													99		

Note:
N/A - Not Available

Table 2. Dissolution Results for Fosamprenavir Tablets, 700 mg used in Study APV10006 and APV10015

Batch No. and Variant (Scale)	% Fosamprenavir Released														
E00B149 (A)	Tablet Number														
Time (Min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	Min	Max
5													12		
10													32		
15													55		
20													75		
25													91		
30													98		
35													100		
40													100		
45													100		

APPEARS THIS WAY
ON ORIGINAL

Dissolution Results for Fosamprenavir Tablets, 700 mg used in Study APV10006 and APV10015 (Cont'd)

Batch No. and Variant (Scale)	% Fosamprenavir Released														
B037578 (B)	Tablet Number														
Time (Min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	Min	Max
5													18		
10													53		
15													81		
20													93		
25													97		
30													98		
35													98		
40													98		
45													98		

Dissolution Results for Fosamprenavir Tablets, 700 mg used in Study APV10006 and APV10015 (Cont'd)

Batch No. and Variant (Scale)	% Fosamprenavir Released														
B050889 (C)	Tablet Number														
Time (Min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	Min	Max
5													17		
10													47		
15													84		
20													94		
25													97		
30													98		
35													98		
40													98		
45													99		

Table 3. Dissolution Results for Fosamprenavir Tablets, 700 mg Batch B083969
[redacted] Production Scale)

Batch No. and Variant	% Fosamprenavir Released														
B083969 (A)	Tablet Number														
Time (Min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	Min	Max
5													21		
10													52		
15													79		
20													94		
25													98		
30													99		
35													99		
40													99		
45													99		

Table 4. Dissolution Results for Fosamprenavir Tablets, 700 mg Batch B084049
[redacted] Production Scale)

Batch No. and Variant	% Fosamprenavir Released														
B084049 (A)	Tablet number														
Time (min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	Min	Max
5													28		
10													62		
15													92		
20													97		
25													98		
30													98		
35													98		
40													98		
45													98		

Table 5. Dissolution Results for Fosamprenavir Tablets, 700 mg Batch E00B223
[redacted] Scale)

Batch No. and Variant	% Fosamprenavir Released														
E00B223 (A)	Tablet Number														
Time (Min)	1	2	3	4	5	6	7	8	9	10	11	12	Mean	Min	Max
5	[redacted]												19		
10													56		
15													92		
20													98		
25													99		
30													99		
35													99		
40													99		
45													99		

Table 6. Dissolution Data for Batch Number E00B149 (Variant A)

	Fosamprenavir Released (% label claim)
	Tablet Number
Time, min	[redacted]
5	
10	
15	
20	
25	
30	
35	
40	
45	
50	
55	
60	

	Fosamprenavir Released (% label claim)														
	Tablet Number														
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5	[redacted]												2	82.6		
10													7	45.9		
15													15	36.4		
20													21	33.4		
25													27	32.2		
30													31	31.7		
35													56	21.1		
40													71	13.9		
45													77	11.5		
50													80	10.3		
55													82	9.7		
60													83	9.1		

Table 7. Dissolution data for Batch Number B083969 (Variant A)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													2	118.2		
10													11	49.7		
15													19	35.5		
20													25	30.4		
25													31	27.4		
30													35	25.0		
35													50	21.0		
40													62	16.1		
45													70	13.1		
50													74	12.0		
55													77	11.1		
60													79	10.4		

Table 8. Dissolution data for Batch Number B084049 (Variant A)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													3	65.1		
10													13	40.4		
15													22	33.5		
20													28	32.2		
25													33	29.7		
30													37	27.3		
35													55	21.0		
40													66	16.2		
45													73	13.0		
50													76	11.4		
55													78	10.3		
60													79	9.6		

Table 9. Dissolution data for Batch Number B084050 (Variant A)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)														
	Tablet Number														
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													1	116.2		
10													10	55.6		
15													19	43.7		
20													25	40.7		
25													30	38.4		
30													34	36.5		
35													50	29.9		
40													64	20.5		
45													71	15.4		
50													75	13.2		
55													78	12.1		
60													80	11.3		

Table 10. Dissolution data for Batch Number B037578 (Variant B)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)														
	Tablet Number														
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													3	65.9		
10													10	39.5		
15													16	32.3		
20													21	30.0		
25													25	27.5		
30													27	26.4		
35													44	22.0		
40													55	18.3		
45													62	15.4		
50													66	13.8		
55													69	12.6		
60													71	11.9		

Table 11. Dissolution data for Batch Number B050889 (Variant C)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													3	62.7		
10													12	33.1		
15													18	25.4		
20													23	21.5		
25													26	19.7		
30													29	18.8		
35													44	18.9		
40													56	18.1		
45													65	14.1		
50													70	11.9		
55													72	10.6		
60													74	9.7		

Table 12. Dissolution Data for Batch Number B104371 (Variant A)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													2	73.7		
10													9	46.7		
15													15	36.3		
20													21	31.9		
25													26	30.1		
30													30	29.8		
35													53	23.7		
40													66	18.7		
45													72	16.2		
50													75	15.1		
55													77	14.2		
60													79	13.2		

Table 13. Dissolution Data for Batch Number B104372 (Variant A)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													1	72.0		
10													6	60.3		
15													13	43.1		
20													19	35.3		
25													24	31.3		
30													28	28.9		
35													48	22.8		
40													60	15.3		
45													68	11.8		
50													71	10.8		
55													73	10.3		
60													75	9.8		

Table 14. Dissolution Data for Batch Number B104926 (Variant A)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													1	100.5		
10													8	50.0		
15													15	35.5		
20													21	30.2		
25													25	29.0		
30													29	28.9		
35													49	24.6		
40													62	16.7		
45													69	12.9		
50													73	11.3		
55													75	10.2		
60													77	9.5		

Table 15. Dissolution Data for Batch Number B104927 (Variant A)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													1	104.2		
10													8	57.7		
15													14	38.3		
20													20	31.4		
25													24	26.4		
30													27	26.8		
35													45	21.2		
40													59	11.4		
45													66	9.1		
50													71	8.2		
55													73	7.8		
60													75	7.5		

Table 16. Dissolution data for Batch Number B044762 (Variant B)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													2	64.1		
10													8	42.3		
15													14	35.4		
20													19	32.8		
25													23	30.9		
30													26	29.4		
35													44	24.4		
40													58	16.9		
45													65	13.9		
50													69	12.5		
55													71	11.7		
60													73	11.3		

Table 17. Dissolution data for Batch Number B065266 (Variant C)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													0	628 9		
10													12	54 4		
15													24	32 5		
20													34	30.3		
25													40	30.9		
30													45	31.1		
35													63	26 1		
40													71	21.8		
45													76	16 8		
50													79	14.2		
55													81	12.9		
60													82	12 0		

Table 18. Dissolution data for Batch Number B065268 (Variant C)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													3	115 5		
10													14	49 4		
15													24	32 6		
20													31	28.6		
25													37	26.5		
30													41	25 1		
35													59	22.7		
40													69	16.3		
45													74	13 4		
50													77	11.7		
55													79	10 6		
60													81	9.6		

Table 19. Dissolution data for Batch Number B081400 (Variant C)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													2	124.0		
10													15	60.5		
15													25	47.7		
20													34	41.7		
25													39	38.3		
30													44	36.2		
35													60	25.7		
40													68	20.4		
45													73	17.7		
50													75	16.2		
55													77	15.2		
60													78	14.5		

Table 20. Dissolution data for Batch Number B081401 (Variant C)

	Fosamprenavir Released (% label claim)											
	Tablet Number											
Time, min	1	2	3	4	5	6	7	8	9	10	11	12
5												
10												
15												
20												
25												
30												
35												
40												
45												
50												
55												
60												

	Fosamprenavir Released (% label claim)															
	Tablet Number															
Time, min	13	14	15	16	17	18	19	20	21	22	23	24	Mean	RSD, %	Minimum	Maximum
5													2	92.4		
10													14	45.3		
15													23	38.3		
20													29	36.2		
25													35	34.7		
30													39	33.5		
35													57	25.9		
40													68	17.8		
45													73	14.5		
50													76	12.8		
55													78	11.7		
60													80	10.9		

6.2 Pharmacometrics Review

Please refer to Dr. Gene Williams' pharmacometrics review of this NDA in a separate document that was submitted to DFS on October 17, 2003.

6.3 Cover Sheet and OCPB Filing /Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-548	Brand Name	LEXIVA
OCPB Division (I, II, III)	DPE III	Generic Name	Fosamprenavir calcium
Medical Division	HFD-530	Drug Class	HIV protease inhibitor (amprenavir pro-drug)
OCPB Reviewer	Derek Zhang	Indication(s)	HIV infection
OCPB Team Leader	Kellie Reynolds	Dosage Form	Tablet (700 mg)
		Dosing Regimen	1400 mg bid or 1400 qd with 200 mg ritonavir qd or 700 mg bid with 100 mg ritonavir bid
Date of Submission	December 19, 2002	Route of Administration	Oral
Estimated Due Date of OCPB Review	September 19, 2003	Sponsor	GSK
PDUFA Due Date	October 20, 2003	Priority Classification	Standard Review
Division Due Date	September 19, 2003		

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	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:		1		02ARS0078
Blood/plasma ratio:				
Plasma protein binding:		3		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:		1		RM2002/00370/00 (PPK)

Patients-				
single dose:				
multiple dose:	X	4		RM2002/00370/00 (PPK), APV20001, APV30002, APV30003
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	5		APV10009, APV10010, APV10011, APV10012, APV10007, APV10022
In-vivo effects of primary drug:		3		APV10011, APV10012, APV10013, APV10022
In-vitro:				
Subpopulation studies -				
ethnicity:		2		APV20001, APV30003
gender:		2		APV20001, APV30003
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:		2		APV30002, APV30003
Population Analyses -				
Data rich:		1		APV20001
Data sparse:		1		RM2002/00370/00 (PPK)
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:		3		APV10004, APV10008, APV10016
alternate formulation as reference:		2		APV10001, APV10002
Bioequivalence studies -				
traditional design; single / multi dose:		2		APV10006, APV10015, APV10021
replicate design; single / multi dose:				
Food-drug interaction studies:	X	4		APV10002, APV10004, APV10008, APV10016
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Other Studies		2		02ARS0078, RD20020093500
Pediatric development plan				

Literature References		14		
Total Number of Studies		23		

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 ?	Discussed with the sponsor about the implications of the fosamprenavir - Kaletra drug interaction studies	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	1. How does amprenavir exposure following fosamprenavir administration compare to amprenavir exposure following Agenerase administration? 2. Are adequate drug interaction data provided?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR

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

/s/

Derek Zhang
10/20/03 01:00:00 PM
BIOPHARMACEUTICS

Kellie Reynolds
10/20/03 01:08:54 PM
BIOPHARMACEUTICS