CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-548

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21548	Submission Date(s): December 19, 2002, April 30, 2003 and May 21, 2003
Brand Name	LEXIVA™
Generic Name	Fosamprenavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie Reynolds, Pharm.D.
Pharmacometric Reviewer	Gene Williams, Ph.D.
OCPB Division	DPE III
OND division	DAVDP
Sponsor	GlaxoSmithKline
Relevant IND(s)	58,627
Submission Type; Code	Standard (1S)
Formulation; Strength(s)	700 mg tablets
Indication	Treatment of HIV infection in combination with other antiretrovial drugs

1 Executive Summary

The sponsor submitted a New Drug Application for LEXIVA (fosamprenavir) for the treatment of HIV-1 infection. This application seeks approval of the following regimens for LEXIVA in combination with other antiretroviral agents:

- In Therapy-Naive Patients: 1,400 mg twice daily (without ritonavir)
  700 mg twice daily plus ritonavir 100 mg twice daily
  1,400 mg once daily plus ritonavir 200 mg once daily
- In Protease Inhibitor-Experienced Patients: 700 mg twice daily plus ritonavir 100 mg twice daily

Fosamprenavir is the calcium salt of the phosphate ester prodrug of amprenavir, an inhibitor of human immunodeficiency virus (HIV) protease. Fosamprenavir was developed as an improved formulation for delivery of amprenavir (APV) to reduce the pill burden of the current formulation of APV (Agenerase, AGN).

1.1 Recommendation

The clinical pharmacology and biopharmaceutics information provided by the sponsor is acceptable. There are no major clinical pharmacology and biopharmaceutics issues related to the approval of this application. The following two concerns have been resolved during the NDA review cycle.

In study APV10015, the sponsor assessed the bioequivalence of fosamprenavir oral film-coated 700mg tablet variants (tablet variants A, B, and C) administered in the pivotal Phase III studies (APV30001, APV30002 and APV30003). APV30001 and APV30002 were conducted with tablets A, B and A/B only. APV30003 was initiated with either tablet A or B but subjects were switched to

tablet C. The sponsor's original plan was to market tablet variant C. The formulation of 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. Tablets B and C were manufactured at [redacted] scale with [redacted] drug substance manufactured at [redacted] scale, respectively. APV10015 demonstrated that tablet variants B and C were 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. This unexpected outcome resulted in a reassessment of the sponsor's original plan to market variant C. At this time, the sponsor plans to only market variant A with [redacted] drug substance manufactured at [redacted] scale in the U.S. The sponsor later conducted study APV10021 to assess bioequivalence between the proposed commercial variant A tablet and the variant A tablet used in the pivotal Phase III studies. Bioequivalence was established.

The sponsor proposed to extrapolate the existing drug interaction data in the Agenerase label to the LEXIVA label based on the following arguments:

- Fosamprenavir is the phosphate ester prodrug of amprenavir. In humans, fosamprenavir is rapidly and extensively converted to APV at or near the intestinal epithelium via alkaline phosphatase, with minimal plasma fosamprenavir exposure (fosamprenavir AUC <0.6% of corresponding APV AUC).
- Equimolar doses of fosamprenavir (i.e. 1400mg) and AGN (i.e. 1200mg) delivered comparable plasma APV exposures (AUC).
- When cross-study comparisons were made between comparable fosamprenavir/RTV and AGN/RTV regimens, plasma APV exposures were similar. These results suggest that RTV has similar effects on plasma APV PK when co-administered with either fosamprenavir or AGN, although these comparisons include data from both healthy and HIV-infected subjects and utilize different plasma PK sampling schemes.

Nevertheless, the review team believed that a drug interaction study to allow a comparison of RTV effects on fosamprenavir versus AGN under identical conditions (same study population and same PK sampling scheme) was warranted to extrapolate the drug interaction data in the Agenerase label to the fosamprenavir label. At the FDA's request, the sponsor conducted study APV10022. The results from this study demonstrated that plasma APV PK parameters were increased to a similar extent when either fosamprenavir or AGN was coadministered with RTV. These data support the extrapolation of AGN drug-drug interaction data to the LEXIVA label.

The outstanding issues that need to be addressed are listed in the Phase IV Commitments Section.

1.2 Phase IV Commitments

1. Fosamprenavir/ritonavir regimens can not be recommended to patients with mild and moderate hepatic impairment (Child-Pugh score ranging from 5 to 8), because they have not been evaluated in this patient population.

- Evaluate pharmacokinetics and safety of fosamprenavir when coadministered with ritonavir in HIV-infected patients with mild and moderate hepatic impairment. Develop dose recommendations for fosamprenavir/ritonavir combination in this patient population.

2. Appropriate doses of the combination with respect to safety and efficacy have not been established for fosamprenavir or fosamprenavir/ritonavir when coadministered with atazanavir.

- Evaluate pharmacokinetics and safety of fosamprenavir or fosamprenavir/ritonavir when coadministered with atazanavir and establish appropriate dose recommendations for the combination with respect to safety and efficacy.

3 Antacids and H_2-receptor antagonists decrease amprenavir concentrations following administration with Lexiva. The sponsor did not evaluate the potential for an interaction with proton pump inhibitors.

- Conduct a human drug-drug interaction study of fosamprenavir calcium twice daily and a proton pump inhibitor, and fosamprenavir calcium/ritonavir twice daily and a proton pump inhibitor.

Although not listed as phase IV commitments, the sponsor also agreed to continue evaluating underlying mechanisms of the drug interaction between fosamprenavir and lopinavir/ritonavir and to continue to evaluate amprenavir's role as a CYP3A4 inducer.

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Fosamprenavir is the calcium salt of the phosphate ester prodrug of amprenavir (approved HIV protease inhibitor, Agenerase) and has been evaluated for safety and efficacy in HIV infected subjects. The approved dose regimens for Agenerase are 1,200 mg twice daily in combination with other antiretroviral agents or 1,200 mg with ritonavir 200 mg once daily, or 600 mg with ritonavir 100 mg twice daily. Fosamprenavir 1,400 mg is an equimolar dose for Agenerase 1,200 mg. Clinical efficacy and safety studies of fosamprenavir were conducted because amprenavir Cmax is lower following administration of fosamprenavir compared to Agenerase.

The clinical pharmacology and biopharmaceutical profiles of fosamprenavir have been defined in healthy and HIV-infected subjects. These studies show fosamprenavir has the following characteristics:

- In humans, fosamprenavir is almost entirely (99%) converted to APV at or near the intestinal epithelium via alkaline phosphatase. Human data confirmed that fosamprenavir is rapidly and extensively converted to APV with minimal plasma fosamprenavir exposure (fosamprenavir AUC <0.6% of corresponding APV AUC).

- Equimolar doses of fosamprenavir (i.e. 1395 or 1400mg) and AGN (i.e. 1200mg) delivered comparable plasma APV exposures except lower Cmax values by fosamprenavir (Data table from study APV20001 (Fosamprenavir a.k.a. GW433908))

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	42.3	24.6
C_{max} (µg/mL)	4.64	7.94	7.19
t_{max} (h)[b]	2.5	2.0	1.3
$t_{1/2}$ (h)[a]	7.7	7.9	9.6
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	17.0	16.2
$C_{max,ss}$ (µg/mL)	4.82	4.78	6.80
$t_{max,ss}$ (h)[b]	1.3	1.5	1.0
$C_{\tau,ss}$ (µg/mL)	0.35	0.35	0.26

- Single dose plasma APV PK is not predictive of steady-state plasma APV PK. Similar to observations in prior AGN studies, plasma APV AUC values decreased over time following multiple-dose administration of fosamprenavir, until reaching steady state in two weeks.

- There were three oral film-coated 700mg tablet variants administered in the pivotal Phase III studies (tablet variants A, B, and C). The majority of phase III studies, particularly the unboosted regimens, used tablet variant A. The sponsor's original plan was to market tablet variant C. The formulation of the tablets was the same; however, the drug substance and drug product manufacturing scales and [redacted] differed. Tablet A was manufactured at [redacted] scale with [redacted] drug substance manufactured at [redacted] scale. Tablets B and C were manufactured at [redacted] scale with [redacted] drug substance manufactured at [redacted] scale, respectively. APV10015 demonstrated that both tablet variants B and C were 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. This unexpected outcome resulted in a reassessment of sponsor's original plan to market variant C. At this time, the sponsor plans to only market variant A with [redacted] drug substance manufactured at [redacted] scale in the U.S. The sponsor later conducted study APV10021 to assess bioequivalence between the proposed commercial variant A tablet and the variant A tablet used in the pivotal Phase III studies. Bioequivalence was established.

  - For tablet variant A, bioequivalence was established between three 465mg tablets and two 700mg tablets. The 465mg- and 700mg-strength oral film-coated tablets were used in the pivotal Phase III studies and the 700mg oral film-coated tablet is the intended market tablet formulation.

- Fosamprenavir tablets may be administered without regard to food intake. When the intended market fosamprenavir oral film-coated 700mg tablet was coadministered with a high-fat meal, plasma APV Cmax and AUC values were not changed, but there was a slight delay of approximately 0.5 hours in tmax.

    - Because RTV exposure is not significantly affected by food intake, plasma APV exposure is similar when fosamprenavir + RTV is administered with food as compared to coadministration in the fasted state. Plasma APV exposures achieved in two studies, APV10011 and APV10012, where fosamprenavir 700mg BID + RTV 100mg BID was administered with food, were similar as compared to concentrations in two studies, APV10010 and APV10013, where the same fosamprenavir/RTV BID regimen was administered under fasting conditions.

- The human pharmacology of APV as previously described for AGN are applicable to fosamprenavir. Pertinent information includes:

    - APV is a CYP3A4 substrate and inhibitor, and potentially a mild CYP3A4 inducer.
    - APV is extensively metabolized by CYP3A4 with minimal unchanged APV excreted in urine.
    - APV is widely distributed in body tissues and is bound to plasma proteins, primarily α1-acid glycoprotein (AAG), by approximately 90%.
    - APV is a substrate for P-glycoprotein.

- The PK interaction between fosamprenavir and RTV is similar to the interaction between AGN and RTV. These data support the extrapolation of AGN drug-drug interaction data to fosamprenavir.

    - Coadministration of fosamprenavir with RTV increases plasma APV exposure (AUC and C_{min} increased by 50% and 4 to 6-fold on average, respectively) primarily through inhibition of APV metabolism.
    - Three dosage regimens, fosamprenavir 1400mg BID, fosamprenavir 700mg BID + RTV 100mg BID, and fosamprenavir 1400mg QD + RTV 200mg QD were selected for the pivotal Phase III clinical studies based on clinical PK, safety and efficacy data generated for equimolar AGN and AGN/RTV regimens.

- APV is a CYP3A4 substrate and inhibitor, and potentially a mild CYP3A4 inducer. Thus, caution should be exercised when co-administering substrates, inducers or inhibitors of CYP3A4 enzyme with fosamprenavir or fosamprenavir/RTV.

    - Coadministration of LEXIVA with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. These drugs are ergot derivatives (dihydroergotamine, ergonovine, ergotamine and methylergonovine), GI motility agent (cisapride), neuroleptic (pimozide), and sedatives/hypnotics (midazolam and triazolam).

    - Rifampin and St. John's wort should not be used in combination with LEXIVA because they reduce plasma concentrations of amprenavir to suboptimal levels and may lead to loss of virologic response and possible resistance to LEXIVA (known for rifampin and assumed for St. John's wort).

    - Concomitant use of LEXIVA with lovastatin or simvastatin is not recommended. Caution should be exercised if LEXIVA is used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis, may be increased when LEXIVA is used in combination with these drugs.

- Caution should be used when prescribing sildenafil or vardenafil in patients receiving LEXIVA. Coadministration of LEXIVA with sildenafil or vardenafil is expected to substantially increase sildenafil or vardenafil concentrations and may result in an increase in sildenafil- or vardenafil associated adverse events, including hypotension, visual changes, and priapism.

- Fosamprenavir solubility is significantly reduced at pH greater than 5. Coadministration of fosamprenavir with Maalox TC and ranitidine, which increase gastrointestinal pH, resulted in reductions in plasma APV exposure (AUC and C_{max}). The mechanism is likely due to changes in gastric pH and phosphate binding that could affect fosamprenavir solubility and subsequent plasma APV pharmacokinetics. The clinical relevance of this drug-drug interaction is not clear. However, caution should be used since fosamprenavir may be less effective due to decreased amprenavir plasma concentrations in patients taking antacids, histamine H_2-receptor antagonists and proton-pump inhibitors concomitantly.

- Plasma APV and LPV exposures markedly decreased when LPV/RTV was coadministered with either fosamprenavir or Agenerase. The interactions for fosamprenavir and amprenavir seem similar, however the underlying mechanisms remain unknown (Please refer to Discussion section in study report APV10011).

- Based on a study of Agenerase, dose reduction is recommended in patients with mild and moderate hepatic impairment because plasma APV concentrations are increased. No dosage recommendation can be given for patients with severe hepatic impairment given the high tablet strength. The fosamprenavir/ritonavir regimens can not be recommended to this patient population because they have not been evaluated.

- No dosage regimen adjustments are recommended for patients with renal dysfunction because APV is extensively metabolized, with <1.3% of an AGN dose excreted in the urine as APV.

- Plasma APV PK is similar based on demographic factors such as sex, race, age, and body weight.

- Plasma APV PK is similar between healthy and HIV-infected adults.

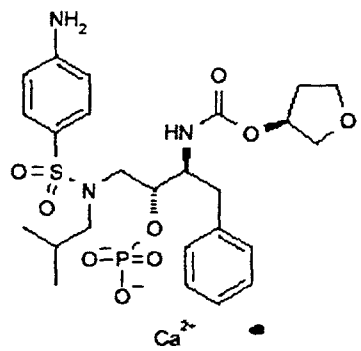
4 Question Based Review

4.1 General Attributes

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

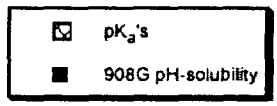
The chemical name of fosamprenavir calcium is (3S)-tetrahydrofuran-3-yl (1S, 2R)-3-[[(4-aminophenyl) sulphonyl] (isobutyl) amino]-1- benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt. Fosamprenavir calcium is a single stereoisomer with the (3S) (1S, 2R) configuration. It has a molecular formula of $C_{25}H_{34}CaN_3O_9PS$ and a molecular weight of 623.7. The molecular weight of fosamprenavir free acid is 585.6. The molecular weight of amprenavir free base is 505.6.

Structural Formula



The pH-solubility profile of fosamprenavir calcium is that of an ampholyte having maximal solubility at pH 3.6 (———), and lower solubility at pH 1.5 (———) and pH 7.1 (———). Fosamprenavir calcium has four ionisation constants, three of which fall within the physiological pH range: pK1 of 1.4, the ionization constant of the aniline amine group; pK2 of 1.6, the first ionization constant of the phosphoric acid which is the salt forming group (at pHs below pK2 the free acid predominates and at pHs above this, the salt forms predominate); and pK3 of 6.3, the second ionization constant of the phosphoric acid moiety.

pH Solubility Profile for Fosamprenavir Calcium



The quantitative composition of Fosamprenavir Tablets, 700 mg is given below:

Composition of Fosamprenavir Tablets, 700 mg

Component	Quantity (mg/tablet)	Function	Reference to Standard
Tablet Core			
Fosamprenavir calcium	[redacted]	Active	GlaxoSmithKline
Microcrystalline Cellulose	[redacted]	[redacted]	USNF
Croscarmellose Sodium	[redacted]	[redacted]	USNF
Povidone K30	[redacted]	[redacted]	USP
Magnesium Stearate	[redacted]	[redacted]	USNF
Colloidal Silicon Dioxide	[redacted]	[redacted]	USNF
[redacted]	[redacted]	[redacted]	USP
Target [redacted] Weight		-	-
Film Coat			
[redacted]	[redacted]	[redacted]	Supplier
[redacted]	-	[redacted]	USP
Target Film-Coated Tablet Weight	[redacted]	-	-

Notes:

1. Equivalent to 700 mg of fosamprenavir. The stated quantity of fosamprenavir calcium assumes [redacted]
2. Quantity may be adjusted to maintain the target [redacted] weight of [redacted]
4. Information relating to this material is provided via DMF No [redacted]
5. [redacted]

4.1.2 What is the proposed mechanism of drug action and therapeutic indication?

Fosamprenavir is the calcium phosphate ester prodrug of APV that is rapidly hydrolyzed to APV and inorganic phosphate as it is absorbed through the gut epithelium. Amprenavir is a potent and selective inhibitor of the HIV-1 aspartyl protease. Fosamprenavir is indicated in combination with other antiretroviral agents for the treatment of HIV infection.

4.1.3 What is the proposed dosage and route of administration?

Fosamprenavir may be taken with or without food. The recommended oral doses of fosamprenavir, alone or in combination with ritonavir, are as follows: In therapy-naive patients: 1,400 mg twice daily (without ritonavir) or 700 mg twice daily plus ritonavir 100 mg twice daily, or 1,400 mg once daily plus ritonavir 200 mg once daily; In protease inhibitor-experienced patients: 700 mg twice daily plus ritonavir 100 mg twice daily.

The dosage should be reduced in patients with mild and moderate hepatic impairment. Patients with a Child-Pugh score ranging from 5 to 8 should receive a dose of fosamprenavir of 700 mg twice daily (without ritonavir). Fosamprenavir should not be used in patients with severe hepatic impairment (Child-Pugh score ranging from 9 to 12) because the dose cannot be reduced below 700 mg. Fosamprenavir/ritonavir regimens can not be recommended to this patient population, because they have not been evaluated.

4.1.4 What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data?

Three pivotal Phase III studies provide safety and efficacy data.

- APV30001 - a 48 week open label, controlled trial comparing fosamprenavir 1400mg BID versus nelfinavir (NFV) 1250mg BID, when administered in combination with abacavir (ABC) 300mg BID and lamivudine (3TC) 150mg BID, to antiretroviral therapy-naïve adult patients infected with HIV-1.

- APV30002 - a 48 week open-label, controlled trial comparing fosamprenavir 1400mg QD/ritonavir (RTV) 200mg QD versus nelfinavir 1250mg BID, when administered in combination with abacavir 300mg BID and lamivudine 150mg BID, to antiretroviral therapy-naïve adult patients infected with HIV-1

- APV30003 - a 48 week open label, controlled trial comparing two dosing regimens of fosamprenavir/ritonavir (700mg/100mg BID and 1400mg/200mg QD) versus lopinavir (LPV)/ritonavir 400mg/100mg BID, when administered in combination with 2 active RTIs, to protease inhibitor-experienced adult patients experiencing virological failure with a previous combination therapy.

Safety:

The most frequent AEs regardless of grade and causality occurring in fosamprenavir-treated subjects were nausea, diarrhea, headache and vomiting. The most common (>4%) drug related grade 2-4 AEs were drug hypersensitivity (abacavir HSR), rash, diarrhea, nausea, and vomiting.

Please refer to Medical Officer, Mr. Russ Fleischer's review on efficacy and safety data.

4.2 General Clinical Pharmacology

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

In antiretroviral-naïve patients, the ability of a treatment regimen to produce maximal viral suppression (reducing plasma HIV-1 RNA below the limit of assay quantitation) is an appropriate test to demonstrate a difference between treatment groups. As such, the proportion of subjects with plasma HIV-1 RNA less than 400 copies/mL was the primary endpoint for clinical trials APV30001 and APV30002. In therapy-experienced subjects, a quantitative change in plasma HIV-1 RNA levels is an alternative choice for the primary end-point. The absolute change in plasma HIV-1 RNA levels from baseline and time averaged area under the plasma HIV-1 RNA-time curve minus baseline (AAUCMB) at weeks 24 and 48 was the primary endpoint for APV30003.

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

The concentrations of fosamprenavir and amprenavir in human plasma were determined by respective validated [redacted] ; methods using [redacted] The assays are acceptable. See section 4.6 for further details. No active metabolites are present in the plasma.

4.2.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety? Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

A wide dose range of fosamprenavir was not evaluated due to the Agenerase data. The relationships between plasma APV PK parameters (Cmax,ss, Cavg,ss, and $C\tau$,ss) and antiviral activity (plasma HIV-1 RNA AAUCMB) assessments over 4 weeks of dosing in antiretroviral-naïve (ART-naïve) subjects were established for AGN in the dose range of 300 mg to 1200 mg BID, and 1200mg BID was selected as the optimal regimen. Plasma APV $C\tau$,ss had the strongest relationship with plasma HIV-1 RNA AAUCMB. Please refer to Drs. Vijay Tammara and Prabhu Rajagopalan's review of Amprenavir (Agenerase) (NDAs 21-007 and 21-039) in 1999.

Fosamprenavir was administered to 78 HIV-infected, anti-retroviral treatment-naïve adult subjects at doses similar to or higher than AGN 1200mg BID in APV20001, a Phase II, multiple-dose, partially-blinded, randomized, crossover study. This study assessed the safety, tolerability, PK, and antiviral activity of two fosamprenavir test regimens, fosamprenavir 1395mg (1200mg APV molar equivalents) BID and fosamprenavir 1860mg (1600mg APV molar equivalents) BID compared to the control regimen, AGN 1200mg BID. All three regimens were administered in combination with ABC 300mg BID and 3TC 150mg BID. All three regimens achieved a similar ~2-log10 copies/mL reduction in plasma HIV-1 RNA concentrations after 4 weeks of dosing; adverse events were generally mild to moderate in intensity and similar among the three dosage regimens. The higher fosamprenavir dosage regimen (1860mg BID) demonstrated similar plasma APV exposure and short-term safety and efficacy as compared to both the lower fosamprenavir 1395mg BID and AGN 1200mg BID regimens, thus, the higher fosamprenavir dosage regimen did not provide additional benefit. Fosamprenavir 1400mg BID was selected for administration in combination with other antiretroviral agents for the treatment of HIV (antiretroviral naïve patients) based on these clinical pharmacology data and confirmed by the pivotal Phase III study APV30001.

The two approved AGN/RTV regimens are AGN 600mg BID + RTV 100mg BID and AGN 1200mg QD + RTV 200mg QD. These regimens were approved based on PK and safety data. Fosamprenavir doses equimolar to these AGN doses have been studied in combination with RTV in the pivotal Phase III studies. Fosamprenavir 1400mg QD + RTV 200mg QD regimen was evaluated in the ART-naïve subjects in study APV30002. In APV30002, plasma APV concentrations were maintained above the IC_{50} for APV against HIV in the ART-naïve subjects. Fosamprenavir 700mg BID + RTV 100mg BID and fosamprenavir 1400mg QD + RTV 200mg QD regimens were administered to the PI-experienced subjects in study APV30003. The individual average plasma APV $C\tau$,ss values were above the baseline IC_{50} for APV against HIV in the PI-experienced subjects. The geometric mean (95% CI) plasma APV $C\tau$,ss values achieved for the fosamprenavir/RTV BID regimen were higher than those for the fosamprenavir/RTV QD regimen. Fosamprenavir 700mg BID + RTV 100mg BID regimen was not investigated in the ART-naïve subjects. However, based on the outcome of this regimen in the PI-experienced subjects and supportive PK data, it is appropriate to recommend this regimen for the ART-naïve subjects.

A dose-relationship was not conclusive with respect to frequency or severity of AEs.

4.2.4 What are the PK characteristics of fosamprenavir?

4.2.4.1 What are the basic PK parameters?

In humans, fosamprenavir is almost entirely (99%) converted to APV at or near the intestinal epithelium via alkaline phosphatase. Fosamprenavir AUC is less than 0.6% of corresponding APV AUC. The pharmacokinetic parameters of amprenavir after administration of LEXIVA (with and without concomitant ritonavir) are shown below.

Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters

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

*Data shown are median (range).

The fosamprenavir studies conducted were designed to determine a dose of fosamprenavir that delivered comparable plasma APV concentrations to AGN. Equimolar doses of fosamprenavir (i.e. 1400mg) and AGN (i.e. 1200mg) delivered comparable plasma APV exposures except lower C_{max} values by fosamprenavir 1400mg.

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	42.3	24.6
C_{max} (µg/mL)	4.64	7.94	7.19
t_{max} (h)[b]	2.5	2.0	1.3
$t_{1/2}$ (h)[a]	7.7	7.9	9.6
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	17.0	16.2
$C_{max,ss}$ (µg/mL)	4.82	4.78	6.80
$t_{max,ss}$ (h)[b]	1.3	1.5	1.0
$C_{\tau,ss}$ (µg/mL)	0.35	0.35	0.26

Fosamprenavir (a.k.a. GW433908)

The fosamprenavir 700mg/RTV 100mg b.i.d. regimen delivers higher plasma APV $AUC_{24,ss}$ (40% ↑), moderately higher $C_{max,ss}$ (18% ↑), and higher $C_{\tau,ss}$ (40% ↑) values compared to the AGN 600mg/RTV 100 mg b.i.d. regimen. However, the difference may be due to the cross-study comparison. The fosamprenavir 1400mg/RTV 200mg once daily regimen delivers almost the same plasma APV $AUC_{24,ss}$, $C_{max,ss}$ and $C_{\tau,ss}$ values compared to the AGN 1200mg/RTV 200 mg once daily regimen.

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	68.2	17.0
$C_{max,ss}$ (μg/mL)	5.16	7.75	6.85
$C_{\tau,ss}$ (μg/mL)[b]	1.51	1.40	0.25

a One subject received AGN 600mg BID + RTV 200mg BID: $AUC_{\tau,ss}$ ~ $C_{max,ss}$ ~ and $C_{\tau,ss}$ ~

b τ = 12 hours for BID regimen and 24 hours for QD regimen.

Single dose plasma APV PK is not predictive of steady-state plasma APV PK. Similar to observations in prior AGN studies, plasma APV AUC values decreased over time following multiple-dose administration of fosamprenavir until achieving steady state approximately on day 14.

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

Plasma APV PK Parameter	GW433908 1395mg BID (N=15)	GW433908 1860mg BID (N=18)[a]	AGN 1200mg BID (N=16)
$AUC_{\tau,ss}/AUC_{\infty}$	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.

The mechanism(s) responsible for time-variant plasma APV PK are unknown but are likely multifactorial. Potential mechanisms are autoinduction of CYP3A4 and P-gp.

A population pharmacokinetic (PK) model was developed for fosamprenavir alone and in combination with ritonavir (RTV). The sponsor conducted a population analysis to support labeling language that pharmacokinetics is "not substantially different" between healthy volunteers and HIV patients. The PM Reviewer concludes that, within the limitations of the small dataset and statistically "un-rigorous" analysis, the desired labeling language is factual. Please refer to Dr. Gene Williams' pharmacometrics review of this NDA. The wording will be included in the label due to previous opinion, the PK differs between healthy volunteers and HIV patients.

4.2.4.2 Does mass balance study suggest the major route of elimination is renal or hepatic?

No mass balance study has been conducted with fosamprenavir. Fosamprenavir is rapidly converted to APV by phosphatase enzymes in the gut epithelium, with very little fosamprenavir available systemically. The principal route of APV elimination is hepatic metabolism by CYP3A4

with subsequent excretion of the metabolites through feces and urine. In a human mass-balance study of [^{14}C]-labeled APV, unchanged drug was below quantifiable amounts in human feces and urine; approximately 75% of the dose was recovered in feces and approximately 14% of the dose was recovered in the urine as oxidative metabolites. Total excretion of APV in the urine over 24-hours ranged from 0.38% to 1.31% of the administered dose over a range of single doses from 150 to 1200 mg. Please refer to Drs. Vijay Tammara and Prabhu Rajagopalan's review of Amprenavir (Agenerase) (NDAs 21-007 and 21-039) in 1999.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? What dosage regimen adjustments, if any, are recommended for each of these subgroups?

4.3.1.1 Age/Gender/Race

The pharmacokinetics of amprenavir do not differ between males and females, or between blacks and non-blacks. Please refer to Drs. Vijay Tammara and Prabhu Rajagopalan's review of Amprenavir (Agenerase) (NDAs 21-007 and 21-039) in 1999.

Correlation analyses were done by various demographic and baseline characteristics including race, sex, age, weight, plasma AAG concentration, hepatitis status, baseline CD4+ cell count, and baseline plasma HIV-1 RNA concentration. Only plasma AAG concentration seems to be correlated with plasma APV AUC and Cmax.

4.3.1.2 Hepatic impairment

No clinical studies have been conducted with fosamprenavir in patients with hepatic impairment. Because fosamprenavir is rapidly converted to APV by phosphatase enzymes in the gut epithelium, with very little fosamprenavir available systemically, dosage recommendations for fosamprenavir in this population are based on the results of the AGN hepatic impairment study. Please refer to Drs. Vijay Tammara and Prabhu Rajagopalan's review of Amprenavir (Agenerase) (NDAs 21-007 and 21-039) in 1999.

Based on AGN dose adjustments for subjects with hepatic impairment and comparable plasma APV exposures (AUC) achieved for equimolar doses of fosamprenavir and AGN, fosamprenavir dosage regimens of 525mg twice daily in subjects with mild and moderate hepatic impairment and 350mg twice daily in subjects with severe hepatic impairment would be appropriate. Considering the available fosamprenavir 700mg tablet strength, the following reduced dosages are recommended in patients with hepatic impairment in order to achieve an exposure similar to the recommended fosamprenavir regimens in subjects without hepatic impairment.

> For subjects with mild and moderate hepatic impairment (Child-Pugh ranging from 5 to 8): fosamprenavir a reduced dosage of 700mg twice daily is recommended. The proposed dosage regimen is predicted to result in plasma APV AUC (6% ↑), Cmax (20% ↓) and Cmin (11% ↑) compared to those achieved with the standard fosamprenavir 1400mg twice daily regimen in patients without hepatic disease.
>
> The 700 mg strength tablet does not support an optimal dosing regimen for subjects with severe hepatic disease (Child-Pugh score ranging from 9 to 15). The predicted Cmin for the 700 mg once daily regimen in this population is about the same as the mean wild-type APV IC_{50}. Thus the 700 mg once daily dosage may lead to loss of virologic response and

possible resistance.

Fosamprenavir/ritonavir regimens can not be recommended to this patient population at this time, because they have not been evaluated. Pharmacokinetic and safety evaluations of fosamprenavir when coadministered with ritonavir in HIV-infected patients with mild and moderate hepatic impairment are needed to develop dose recommendations for fosamprenavir/ritonavir combination in this patient population.

4.3.1.3 Renal impairment

No dosage regimen adjustments are recommended for patients with renal dysfunction because APV is extensively metabolized with only less than 1.3% of an AGN dose excreted in the urine as APV.

4.4 Extrinsic Factors

4.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Refer to Drug-Drug Interactions section (Section 4.4.2) for the potential effects of other drugs on fosamprenavir and of fosamprenavir on other drugs. Refer to Section 4.5.3 for food effect.

4.4.2 Drug-Drug Interactions

4.4.2.1 Is there an in vitro basis to support in vivo drug-drug interactions?

APV is a CYP3A4 substrate and it is extensively metabolized by CYP3A4 with minimal unchanged APV excreted in urine (Please refer to Drs. Vijay Tammara and Prabhu Rajagopalan's review of Amprenavir (Agenerase) (NDAs 21-007 and 21-039) in 1999). APV is also a substrate and likely an inhibitor of P-glycoprotein.

APV is an inhibitor of CYP3A4 at clinically relevant concentrations based on in vitro studies. A side-by-side comparison of APV and other HIV PIs showed the potency of CYP3A4 inhibition to be ritonavir (most potent) >> indinavir ≈ nelfinavir ≈ APV > saquinavir. APV did not inhibit CYP1A2, CYP2B, CYP2C9, CYP2D6, or CYP2E1 activity as measured by inhibition of probe substrates in pooled human liver microsomes. In the same study, APV was a weak inhibitor of CYP2C19 at concentrations (IC_{50}=50 μM, 25 μg/mL) above those observed clinically (0.3-8 μg/mL). Please refer to Drs. Vijay Tammara and Prabhu Rajagopalan's review of Amprenavir (Agenerase) (NDAs 21-007 and 21-039) in 1999.

Fosamprenavir has been studied in combination with low-dose RTV due to the ability of RTV to favorably enhance plasma APV PK. RTV is a more potent CYP3A4 inhibitor than APV based on both in vitro and in vivo data. The dose of RTV that will be recommended for coadministration with fosamprenavir (200 mg/day) is lower than the approved RTV dose (1200 mg/day). RTV also inhibits CYP2D6 and induces CYP3A4, CYP1A2, CYP2C9, and glucuronosyl transferase (see Norvir label).

APV (The full study report has yet to be submitted by the sponsor although we have requested it several times) and RTV have both demonstrated high activation of PXR. PXR, a nuclear receptor, has been identified as a transcriptional regulator of CYP3A and P-gp expression. The PXR assay can identify potential inducers of CYP3A4 and P-gp. However, the in vivo relevance of this assay,

has not been fully established. Other in vitro data from literature also demonstrated APV induction of P-gp in a human intestinal cell line.

In humans, fosamprenavir is almost entirely (99%) converted to APV at or near the intestinal epithelium via alkaline phosphatase. Human data confirmed that fosamprenavir is rapidly and extensively converted to APV with minimal plasma fosamprenavir exposure (fosamprenavir AUC <0.6% of corresponding APV AUC).

Fosamprenavir vs APV Exposure (%) Following Oral Dose of Fosamprenavir (APV20001)

PK Parameter	Mean (SD)
AUC_{last}	0.164 (0.146)
C_{max}	0.485 (0.391)

The pH-solubility profile of fosamprenavir calcium is that of an ampholyte having maximal solubility at pH 3.6 [redacted] and lower solubility at pH 1.5 [redacted] and pH 7.1 [redacted]

Therefore, coadministration of fosamprenavir with drugs that alter fosamprenavir or APV absorption, distribution, metabolism and elimination (ADME) will likely result in changes in plasma APV exposure. Likely mechanisms are inhibition or induction of CYP3A4, inhibition or induction of P-gp, and increases in gastrointestinal pH. On the other hand, caution should be exercised when co-administering drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious adverse events with fosamprenavir or fosamprenavir/RTV. However, in some cases, amprenavir decreases coadministered drugs' plasma exposure likely due to CYP3A4 induction. It may lead to loss of efficacy of the coadministered drugs, such as delavirdine.

4.4.2.2 Is the drug a substrate, an inhibitor or inducer of P-glycoprotein transport process?

An in vitro study with CaCo-2 cells indicated APV is a substrate for P-gp (GSK Document # RD2002/00489/00). Another study examined the distribution of radioactivity after oral administration of [^{14}C]-APV in male P-gp-knockout (mdr-1a/b deficient) and FVB mice (control). Results indicated that the concentrations of APV-related radioactivities were higher in the blood and target tissues (brain and testes) of P-gp-knockout mice than in the control mice (GSK Document # RD2001/00984/00). These results suggest that P-gp may play a role in the absorption and distribution of APV into tissues. APV has also demonstrated induction of P-gp by increases in intestinal P-gp levels in rats and induction of P-gp in a human intestinal cell line.

4.4.2.3 Are there other metabolic/transporter pathways that may be important?

The principal route of APV elimination is hepatic metabolism by CYP3A4 with subsequent excretion of the metabolites through feces and urine. No further study was conducted to evaluate other metabolic/transporter pathways.

4.4.2.4 What interaction data are available? What is the impact?

To allow the appropriate use of fosamprenavir and fosamprenavir/RTV with other drugs that may commonly be administered to HIV-infected patients, fosamprenavir and fosamprenavir/RTV drug interaction studies were conducted to supplement available drug interaction data for AGN. Drug interactions between fosamprenavir and antacid (Maalox TC, aluminum hydroxide/magnesium hydroxide), ranitidine, atorvastatin, and lopinavir/ritonavir were studied; drug interaction studies between the combination of fosamprenavir/RTV and atorvastatin, lopinavir/RTV and efavirenz were also conducted.

As discussed in the previous sections, in humans, fosamprenavir is almost entirely (99%) converted to APV at or near the intestinal epithelium via alkaline phosphatase. Human PK data also confirmed that fosamprenavir is rapidly and extensively converted to APV with minimal plasma fosamprenavir exposure (fosamprenavir AUC <0.6% of corresponding APV AUC). Thus, the sponsor hypothesized that it is appropriate to extrapolate available drug interaction data from the Agenerase label to the fosamprenavir label.

However, there were some concerns with this assumption due to its potential impact. We requested the sponsor conduct a crossover-study (APV10022) to confirm that RTV affected APV to a similar extent following coadministration with fosamprenavir versus AGN. The results of this study demonstrated that PK interaction between fosamprenavir and RTV was similar to the interaction between AGN and RTV. These data support the extrapolation of AGN drug-drug interaction data to fosamprenavir.

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.

Another concern that arose during the NDA review is the implications of the fosamprenavir-Kaletra drug interaction. Plasma APV and LPV exposures markedly decreased when LPV/RTV was coadministered with fosamprenavir. In addition, the combination was not well tolerated in healthy volunteers. Appropriate doses of the combination with respect to safety and efficacy have not been established. The interaction between Agenerase and Kaletra seems similar to that of fosamprenavir and Kaletra. However, the mechanism by which LPV/RTV decreased plasma APV exposure is unknown. The sponsor conducted several preclinical studies to evaluate the mechanism. There does not appear to be a physicochemical interaction between the two products based on similar fosamprenavir release rates during dissolution testing of fosamprenavir in the presence and absence of LPV/RTV. The dissolution profiles for fosamprenavir tablets were comparable in the presence and absence of Kaletra with full release demonstrated within 30 minutes. Neither LPV nor RTV inhibited human intestinal alkaline phosphatase. Thus, alteration of the conversion of fosamprenavir to APV is not a likely mechanism for the decreased plasma APV exposure observed when fosamprenavir is coadministered with LPV/RTV. Based on the knowledge that all three drugs are inhibiters and inducers of CYP3A4 and are substrates for P-gp and that APV and RTV are also P-gp inducers and inhibitors, the sponsor speculates that the mechanism of the interaction between fosamprenavir and LPV/RTV likely involves a complex balance between the induction and inhibition of metabolic and, potentially, transport processes. The mechanisms by which LPV/RTV markedly decreased plasma APV exposure need to be elucidated. We will recommend the sponsor to continue to evaluate the drug-drug interactions

between Kaletra and fosamprenavir/ritonavir and to elucidate the underlying mechanisms. It is not clear whether other drugs may interact with fosamprenavir in the same manner.

The following tables illustrate the summary results of drug-drug interaction studies performed with fosamprenavir.

Pharmacokinetic Parameters for Amprenavir in the Presence of the Coadministered Drug After Administration of Fosamprenavir

Coadministered Drug(s) and Dose(s)	Dose of LEXIVA	n	% Change in Amprenavir Pharmacokinetic Parameters (90% CI)		
			C_{max}	AUC	C_{min}
Antacid (MAALOX TC®)	1,400 mg single dose	30	↓35 (↓24 to ↓42)	↓18 (↓9 to ↓26)	↑14 (↓7 to ↑39)
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↓18 (↓34 to ↑1)	↓27 (↓41 to ↓12)	↓12 (↓27 to ↑6)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	⇔	⇔	⇔
Efavirenz 600 mg q.d. for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	⇔	↓13 (↓30 to ↑7)	↓36 (↓8 to ↓56)
Efavirenz 600 mg q.d. plus additional Ritonavir 100 mg q.d for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	↑18 (↑1 to ↑38)	↑11 (0 to ↑24)	⇔
Efavirenz 600 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	⇔	⇔	↓17 (↓4 to ↓29)
Lopinavir/ritonavir 533 mg/133 mg b.i.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	18	APV exposures with the regimen containing fosamprenavir 1,400 mg b.i.d. + lopinavir/ritonavir 533 mg/133 b.i.d. mg for 2 weeks were much lower than those of the regimen with fosamprenavir 700 mg b.i.d. + ritonavir 100 mg b.i.d. for 2 weeks: Cmax was 13% lower, AUC was 26% lower, and Cmin was 42% lower.		
Lopinavir/ritonavir 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↓58 (↓42 to ↓70)	↓63 (↓51 to ↓72)	↓65 (↓54 to ↓73)
Ranitidine 300 mg single dose	1,400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	⇔ (↓19 to ↑21)

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%).

Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of Fosamprenavir

Coadministered Drugs and Dose(s)	Dose of LEXIVA	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
			C_{max}	AUC	C_{min}
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↑304 (↑205 to ↑437)	↑130 (↑100 to ↑164)	↓10 (↓27 to ↑12)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↑184 (↑126 to ↑257)	↑153 (↑115 to ↑199)	↑73 (↑45 to ↑108)
Lopinavir/ritonavir* 533 mg/133 mg b.i.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	18	LPV exposures with the regimen containing lopinavir/ritonavir 533 mg/133 mg b.i.d. + fosamprenavir 1,400 mg b.i.d. for 2 weeks were similar compared to those of the regimen with lopinavir/ritonavir 400 mg/100 mg b.i.d. for 2 weeks: less than 10% change in Cmax, AUC, and Cmin values.		
Lopinavir/ritonavir* 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↑30 (↓15 to ↑47)	↑37 (↓20 to ↑55)	↑52 (↓28 to ↑82)

*Data represent lopinavir concentrations.
↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%).

The following tables illustrate the summary results of drug-drug interaction studies performed with Agenerase. Please refer to Drs. Vijay Tammara and Prabhu Rajagopalan's review of Amprenavir (Agenerase) (NDAs 21-007 and 21-039) in 1999 for drug interaction data of coadministration with Agenerase.

Pharmacokinetic Parameters for Amprenavir After Administration of AGENERASE in the Presence of the Coadministered Drug

Coadministered Drugs and Dose(s)	Dose of AGENERASE*	n	% Change in Amprenavir Pharmacokinetic Parameters (90% CI)		
			C_{max}	AUC	C_{min}
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↑15 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↑40*	↑130*	↑125*
Ethinyl estradiol/norethindrone 0.035 mg/1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	⇔	↓22 (↓35 to ↓8)	↓20 (↓41 to ↑8)
Indinavir 800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↓16 (↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	⇔	⇔	NA
Nelfinavir 750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	⇔	↑189 (↑52 to ↑448)
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	⇔	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
Saquinavir 800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
Zidovudine 300 mg single dose	600 mg single dose	12	⇔	↑13 (↓2 to ↑31)	NA

* Median percent change; confidence interval not reported.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study.

Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of AGENERASE

Coadministered Drug(s) and Doses	Dose of AGENERASE	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
			C_{max}	AUC	C_{min}
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↓10 (↓24 to ↑7)	⇔	⇔
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↓47*	↓61*	↓88*
Ethinyl estradiol 0.035 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	⇔	⇔	↑32 (↓3 to ↑79)
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↑19 (↑8 to ↑33)	↑44 (↑31 to ↑59)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	⇔	⇔	NA
Methadone 44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16	R-Methadone (active)		
			↓25 (↓32 to ↓18)	↓13 (↓21 to ↓5)	↓21 (↓32 to ↓9)
			S-Methadone (inactive)		
			↓48 (↓55 to ↓40)	↓40 (↓46 to ↓32)	↓53 (↓60 to ↓43)
Norethindrone 1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	⇔	↑18 ↑1 to ↑38	↑45 ↑13 to ↑88
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	⇔	⇔	ND
Zidovudine 300 mg single dose	600 mg single dose	12	↑40 (↑14 to ↑71)	↑31 (↑19 to ↑45)	NA

* Median percent change; confidence interval not reported.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study; ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

Dosing recommendations based on results of fosamprenavir and Agenerase drug interaction studies and the properties of amprenavir and ritonavir: APV is a CYP3A4 substrate and inhibitor, and potentially a mild CYP3A4 inducer. RTV is a more potent CYP3A4 inhibitor than APV. The dose of RTV that will be recommended for coadministration with fosamprenavir (200mg/day) is lower than the marketed RTV dose (1200mg/day). RTV also inhibits CYP2D6 and induces CYP3A4, CYP1A2, CYP2C9, and glucuronosyl transferase (see Norvir label).

Thus, caution should be exercised prior to and during co-administration of substrates, inducers or inhibitors of CYP3A4 enzyme with fosamprenavir or fosamprenavir/RTV.

Drugs That Should Not Be Coadministered with LEXIVA

Drug Class/Drug Name	Clinical Comment
Antiarrhythmics: Flecainide, propafenone	CONTRAINDICATED if LEXIVA is co-prescribed with ritonavir due to potential for serious and/or life threatening reactions such as cardiac arrhythmias secondary to increases in plasma concentrations of antiarrhythmics.
Antimycobacterials: Rifampin	May lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.
Ergot derivatives: Dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agents: Cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to LEXIVA or to the class of protease inhibitors.
HMG co-reductase inhibitors: Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: Pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor: Delavirdine	May lead to loss of virologic response and possible resistance to delavirdine.
Sedative/hypnotics: Midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

Amprenavir is metabolized by CYP3A4. Coadministration of LEXIVA and drugs that induce CYP3A4, such as rifampin, may decrease amprenavir concentrations and reduce its therapeutic effect. Coadministration of LEXIVA and drugs that inhibit CYP3A4 may increase amprenavir concentrations and increase the incidence of adverse effects. The potential for drug interactions with LEXIVA changes when LEXIVA is coadministered with the potent CYP3A4 inhibitor ritonavir. The magnitude of CYP3A4 mediated drug interactions (effect on amprenavir or effect on coadministered drug) may change when LEXIVA is coadministered with ritonavir. Because ritonavir is a CYP2D6 inhibitor, clinically significant interactions with drugs metabolized by CYP2D6 are possible when coadministered with LEXIVA plus ritonavir.

Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction
(Information in the table applies to fosamprenavir with or without ritonavir, unless otherwise indicated.)

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitors: Efavirenz	LEXIVA: ↓Amprenavir LEXIVA plus ritonavir: ↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established. An additional 100 mg/day (300 mg total) of ritonavir is recommended when efavirenz is administered with LEXIVA plus ritonavir once daily. No change in the ritonavir dose is required when efavirenz is administered with LEXIVA plus ritonavir twice daily.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Amprenavir	Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitors: Indinavir, nelfinavir	LEXIVA: ↑Amprenavir Effect on indinavir and nelfinavir is not well established. LEXIVA plus ritonavir: Interaction has not been	Appropriate doses of the combinations with respect to safety and efficacy have not been established.

	evaluated.	
HIV protease inhibitors: Lopinavir/ritonavir	↓Amprenavir ↓Lopinavir	An increased rate of adverse events has been observed with coadministration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV protease inhibitor: Saquinavir	LEXIVA: ↓Amprenavir Effect on saquinavir is not well established. LEXIVA plus ritonavir: Interaction has not been evaluated.	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: Amiodarone, lidocaine (systemic), and quinidine	↑Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with LEXIVA.
Antiarrhythmic: Bepridil	↑Bepridil	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.
Anticoagulant: Warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	↓Amprenavir	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
Antifungals: Ketoconazole, itraconazole	↑Ketoconazole ↑Itraconazole	Increase monitoring for adverse events due to ketoconazole or itraconazole. LEXIVA: Dose reduction of ketoconazole or itraconazole may be needed for patients receiving more than 400 mg ketoconazole or itraconazole per day. LEXIVA plus ritonavir: High doses of ketoconazole or itraconazole (>200 mg/day) are not recommended.
Antimycobacterial: Rifabutin	↑Rifabutin and rifabutin	A complete blood count should be performed weekly and as clinically indicated in order to monitor for

	metabolite	neutropenia in patients receiving LEXIVA and rifabutin. LEXIVA: A dosage reduction of rifabutin by at least half the recommended dose is required when LEXIVA and rifabutin are coadministered. LEXIVA plus ritonavir: Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (a maximum dose of 150 mg every other day or three times per week).
Benzodiazepines: Alprazolam, clorazepate, diazepam, flurazepam	↑Benzodiazepines	Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed.
Calcium channel blockers: Diltiazem, felodipine, nifedipine, nicardipine, nimodipine, verapamil, amlodipine, nisoldipine, isradipine	↑Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: Dexamethasone	↓Amprenavir	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
PDE5 inhibitors: Sildenafil, vardenafil	↑Sildenafil ↑Vardenafil	Use sildenafil with caution at reduced doses of 25 mg every 48 hours with increased monitoring for adverse events. Use vardenafil with caution at reduced doses of no more than 2.5 mg every 24 hour.
Histamine H_2-receptor antagonists and proton-pump inhibitors	LEXIVA: ↓Amprenavir LEXIVA plus ritonavir: Interaction not evaluated	Use with caution. LEXIVA may be less effective due to decreased amprenavir plasma concentrations in patients taking these agents concomitantly.
HMG-CoA reductase inhibitor: Atorvastatin	↑Atorvastatin	Use ≤20 mg/day of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin, fluvastatin, or rosuvastatin in combination with LEXIVA.
Immunosuppressants: Cyclosporine, tacrolimus,	↑Immunosup-pressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered

sirolimus		with LEXIVA.
Narcotic analgesic: Methadone	↓Methadone	Dosage of methadone may need to be increased when coadministered with LEXIVA.
Oral contraceptives: Ethinyl estradiol/ norethindrone	LEXIVA: ↑Ethinyl estradiol/ norethindrone LEXIVA plus ritonavir: Interaction not evaluated	Because hormonal levels may be altered, alternative methods of non-hormonal contraception are recommended.
Tricyclic antidepressants: Amitriptyline, imipramine	↑Tricyclics	Therapeutic concentration monitoring is recommended for tricyclic antidepressants when coadministered with LEXIVA.

4.5 General Biopharmaceutics

4.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The sponsor's original plan was to market tablet variant C. However, bioequivalence was not established amongst the three tablet variants, A, B, and C. Tablet variants B and C (scale) delivered 13-16% lower plasma APV exposure and were not bioequivalent to tablet variant A (APV10015). Please refer to Recommendation section in Executive Summary. The sponsor now plans to market tablet variant A.

PK Parameter	Geometric LS Mean			Ratio of the GLS Means (90% CI)	
	Treatment A	Treatment B	Treatment C	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 drug substance manufactured at scale and tablets manufactured at cale, fasted
Treatment B = Two GW433908 oral film-coated 700mg tablets, drug substance manufactured at scale and tablets manufactured at scale, fasted
Treatment C = Two GW433908 oral film-coated 700mg tablets, drug substance manufactured at scale and tablets manufactured at scale, fasted

Bioequivalence was achieved between the fosamprenavir 700mg oral film-coated tablets (variant A) used in the pivotal Phase III studies and the proposed commercial tablets (variant A, APV10021). Thus, this application is being submitted in support of marketing fosamprenavir 700mg tablets manufactured at scale with drug substance manufactured at scale (tablet variant A).

	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 B083959).			

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

4.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Fosamprenavir tablets may be administered without regard to food intake. When the intended market fosamprenavir oral film-coated 700mg tablet was coadministered with a high-fat meal, plasma APV Cmax and AUC values were not changed but there was a slight delay of approximately 0.5 hours in tmax.

	Geometric LS Mean		Ratio (90% CI)
Plasma APV PK Parameter	Tablet Fasted (Treatment A)	Tablet Fed (Treatment B)	B/A
AUC_{∞} (µg.h/ml)	19.0	19.4	1.02 (0.93-1.12)
C_{max} (µg/ml)	4.25	4.50	1.06 (0.94-1.19)

4.5.3 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The proposed dissolution method and specification for fosamprenavir 700 mg tablet are acceptable. They are as follows:

Apparatus USP II (paddle) with a volume of —
Rotation Speed —
Temperature 37.5°C
Medium —
Sampling Time 30-minute
Analytical Method —

The sponsor proposed dissolution specification for fosamprenavir 700 mg tablet is Q = — dissolved in 30 minutes.

The original proposal was at — timepoint. The sponsor voluntarily tightened the specification due to the previously discussed BE problem. The proposed dissolution method was reviewed by Dr. Jennifer DiGiacinto prior to the NDA submission and agreed on.

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. However, this dissolution method is not able to discriminate tablet variants B and C from 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 using the sponsor's in-house [redacted] model. The [redacted] model 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] described will be conducted initially [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.

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

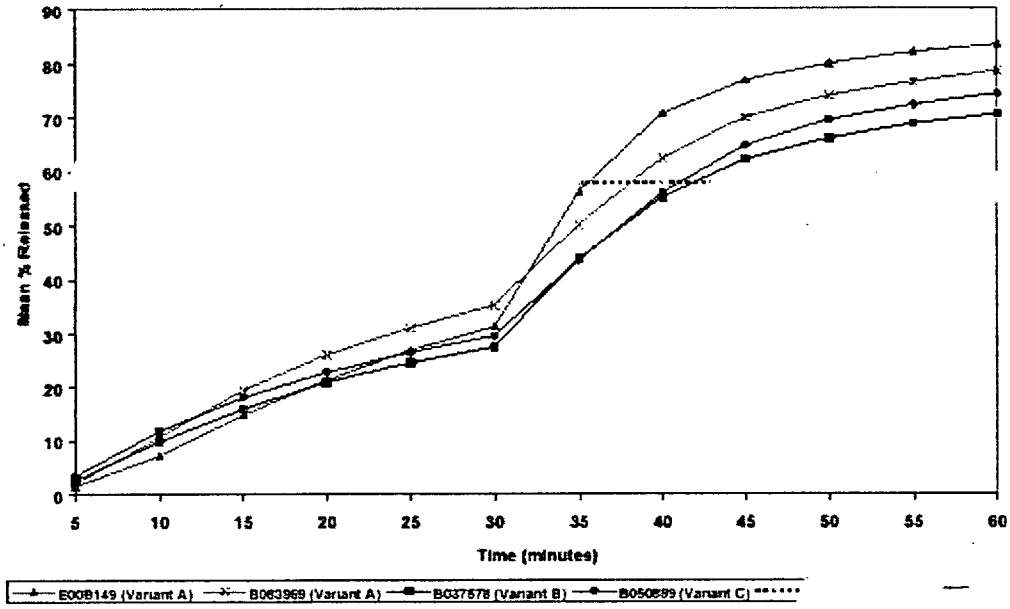
Apparatus	USP II (paddle) with a volume of [redacted]
Rotation Speed	[redacted]
Temperature	37.5°C
Medium 1	[redacted]
Medium 2	[redacted]
Sampling Time	[redacted]
Analytical Method	[redacted]

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

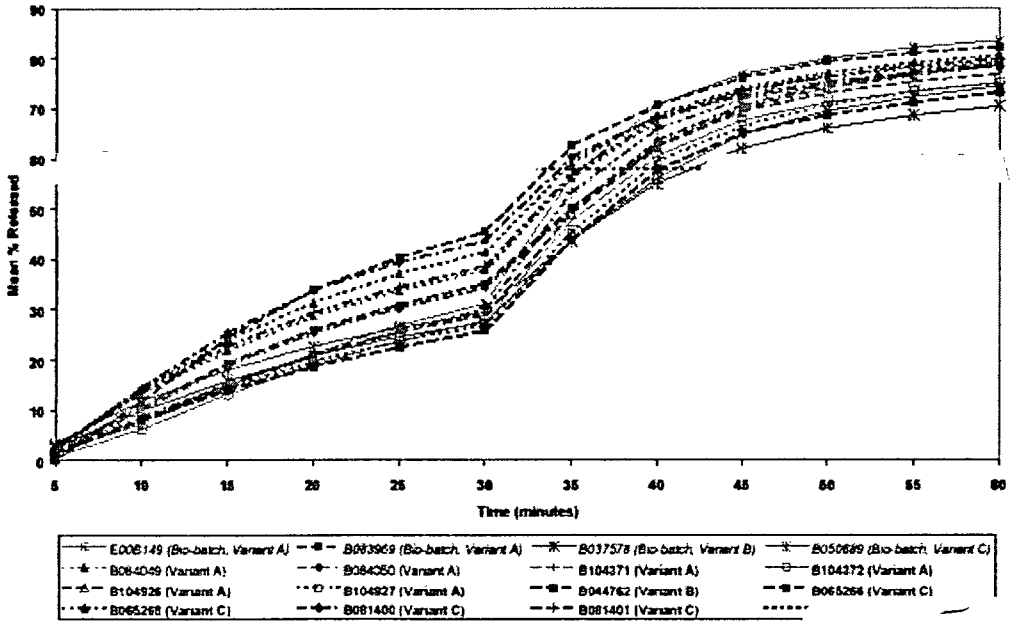
This test appears to discriminate between tablet variant A and tablet variants B and C used in APV10015. The tablet variants A (Batch E00B149), B (Batch B037578) and C (Batch B050889) used in APV10015, and the proposed commercial variant A tablet (Batch B083969) were submitted to the test. Batches of tablet variant A (Batches E00B149 and B083969) passed the specification of [redacted] test. However, neither tablet variant B nor variant C met the specification. These results are consistent with the results observed in bioequivalence studies APV10015 and APV10021.

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. It is not clear that these batches of tablet variants B and C will be bioequivalent to tablet variant A. Based on these data, it is not possible to conclude that this dissolution method will assure the *in vivo* performance.

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



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



4.6 Analytical

4.6.1 Which moieties have been selected for analysis and why?

Both fosamprenavir and APV were selected for analysis. APV is the only active moiety in the systemic circulation after fosamprenavir administration/conversion. Measuring the fosamprenavir plasma concentration provides evidence of extent and rate of fosamprenavir conversion to APV.

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

Total plasma concentrations of fosamprenavir and APV were measured. APV is approximately 90% protein bound, primarily to α 1-acid glycoprotein (AAG). It is appropriate to measure the total plasma concentrations because they represent the plasma exposure of the absorbed drug in the systemic circulation.

4.6.3 What bioanalytical methods are used to assess concentrations?

The following table summarizes the analytical methods used for the determinations of fosamprenavir, APV and other drugs in each study (Listed as the biggest value of %CV in each experiment).

Analyte	Methods	Study	Linear range (ng/mL)	Between Run Precision (%CV) Not less than	Between Run Bias (% Deviation) No less than
Fosamprenavir APV		APV10001			
APV		APV10002			
APV		APV10004			
APV		APV10006			
Fosamprenavir APV		APV10007			
APV		APV10008			
Fosamprenavir APV ritonavir		APV10009			
Fosamprenavir APV ritonavir		APV10010			
APV lopinavir		APV10011			
APV lopinavir		APV10012			
APV Atorvastatin		APV10013			
APV		APV10015			
Fosamprenavir APV		APV10016			
Fosamprenavir APV		APV20001			
APV		APV30002			
APV		APV30003			

The analytical methods are acceptable.

APPEARS THIS WAY
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5 Labeling Recommendations

The revised version of Clinical Pharmacology section of the label is listed below. In addition, Table "Drugs That Should Not Be Coadministered with LEXIVA" on page 22 of this review is and Table "Alteration in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction" on page 23 of this review are listed in the Precautions: Drug Interactions section of the label.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: Fosamprenavir is a prodrug, which is rapidly hydrolyzed to amprenavir by enzymes in the gut epithelium as it is absorbed.

The pharmacokinetic properties of amprenavir after administration of LEXIVA with or without ritonavir, have been evaluated in both healthy adult volunteers and in HIV-infected patients; no substantial differences in steady-state amprenavir concentrations were observed between the 2 populations.

Absorption and Bioavailability: After administration of a single dose of LEXIVA to HIV-1-infected patients, the time to peak amprenavir concentration (T_{max}) occurred between 1.5 and 4 hours (median 2.5 hours). The absolute oral bioavailability of amprenavir after administration of LEXIVA in humans has not been established.

The pharmacokinetic parameters of amprenavir after administration of LEXIVA (with and without concomitant ritonavir) are shown in Table 2.

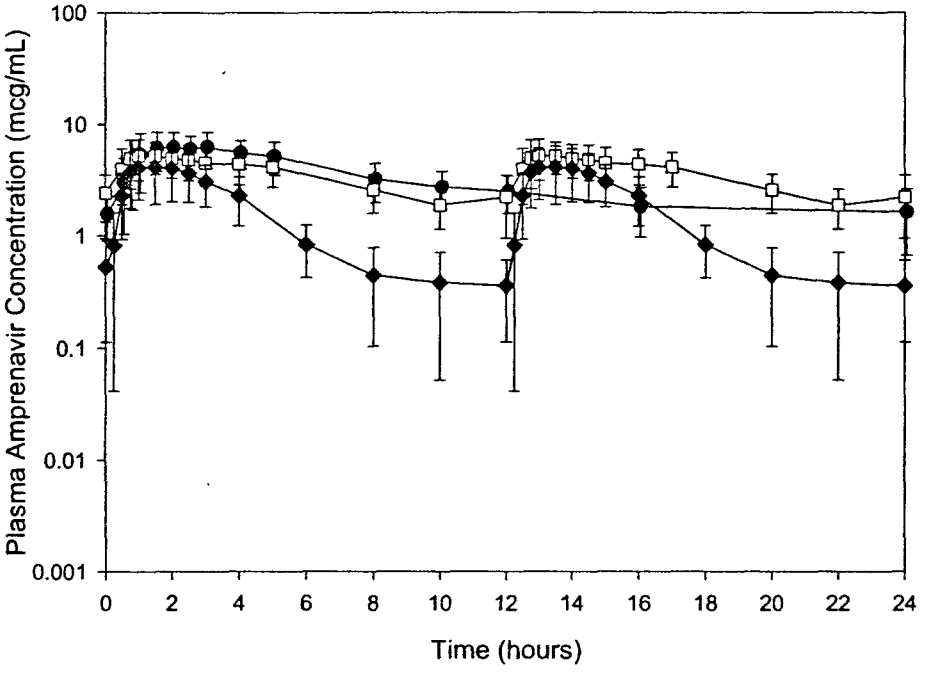
Table 2. Geometric Mean (95% CI) Steady-State Plasma Amprenavir Pharmacokinetic Parameters

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

*Data shown are median (range).

The median plasma amprenavir concentrations of the dosing regimens over the dosing intervals are displayed in Figure 1.

Figure 1: Mean (Standard Deviation) Steady-State Plasma Amprenavir Concentrations and Mean IC_{50} Values Against HIV from Protease Inhibitor-Naive Patients (in the Absence of Human Serum)



Effects of Food on Oral Absorption: LEXIVA Tablets may be taken with or without food (see DOSAGE AND ADMINISTRATION). Administration of a single 1,400-mg dose of LEXIVA in the fed state (standardized high-fat meal: 967 kcal, 67 grams fat, 33 grams protein, 58 grams carbohydrate) compared to the fasted state was associated with no significant changes in amprenavir C_{max}, T_{max}, or $AUC_{0-\infty}$.

Distribution: In vitro, amprenavir is approximately 90% bound to plasma proteins, primarily to $alpha_1$-acid glycoprotein. In vitro, concentration-dependent binding was observed over the concentration range of 1 to 10 ug/mL, with decreased binding at higher concentrations. The partitioning of amprenavir into erythrocytes is low, but increases as amprenavir concentrations increase, reflecting the higher amount of unbound drug at higher concentrations.

Metabolism: After oral administration, fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir and inorganic phosphate prior to reaching the systemic circulation. This occurs in the gut epithelium during absorption. Amprenavir is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The 2 major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in urine and feces.

Elimination: Excretion of unchanged amprenavir in urine and feces is minimal. Unchanged amprenavir in urine accounts for approximately 1% of the dose; unchanged amprenavir was not detectable in feces. Approximately 14% and 75% of an administered single dose of ^{14}C-amprenavir can be accounted for as metabolites in urine and feces, respectivelyTwo

metabolites accounted for >90% of the radiocarbon in fecal samples. The plasma elimination half-life of amprenavir is approximately 7.7 hours.

Special Populations: ***Hepatic Insufficiency:*** The pharmacokinetics of amprenavir after administration of LEXIVA have not been studied in patients with hepatic insufficiency.

The pharmacokinetics of amprenavir have been studied after administration of amprenavir given as AGENERASE Capsules to adult patients with impaired hepatic function using a single 600-mg oral dose. The $AUC_{0-\infty}$ of amprenavir was significantly greater in patients with moderate cirrhosis (25.76 ± 14.68 mcg•hr/mL) compared with healthy volunteers (12.00 ± 4.38 mcg•hr/mL). The $AUC_{0-\infty}$ and C_{max} were significantly greater in patients with severe cirrhosis ($AUC_{0-\infty}$: 38.66 ± 16.08 mcg•hr/mL; C_{max}: 9.43 ± 2.61 mcg/mL) compared with healthy volunteers ($AUC_{0-\infty}$: 12.00 ± 4.38 mcg•hr/mL; C_{max}: 4.90 ± 1.39 mcg/mL). Based on these data, patients with impaired hepatic function receiving LEXIVA without concurrent ritonavir may require dosage reduction. There are no data on the use of LEXIVA in combination with ritonavir in patients with any degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The impact of renal impairment on amprenavir elimination in adult patients has not been studied. The renal elimination of unchanged amprenavir represents approximately 1% of the administered dose; therefore, renal impairment is not expected to significantly impact the elimination of amprenavir.

Pediatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA to pediatric patients are under investigation. There are insufficient data at this time to recommend a dose.

Geriatric Patients: The pharmacokinetics of amprenavir after administration of LEXIVA to patients over 65 years of age have not been studied.

Gender: The pharmacokinetics of amprenavir after administration of LEXIVA do not differ between males and females.

Race: The pharmacokinetics of amprenavir after administration of LEXIVA do not differ between blacks and non-blacks.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.

Amprenavir, the active metabolite of fosamprenavir, is metabolized in the liver by the cytochrome P450 enzyme system. Amprenavir inhibits CYP3A4. Data also suggest that amprenavir induces CYP3A4. Caution should be used when coadministering medications that are substrates, inhibitors, or inducers of CYP3A4, or potentially toxic medications that are metabolized by CYP3A4. Amprenavir does not inhibit CYP2D6, CYP1A2, CYP2C9, CYP2C19, CYP2E1, or uridine glucuronosyltransferase (UDPGT).

Drug interaction studies were performed with LEXIVA and other drugs likely to be coadministered or drugs commonly used as probes for pharmacokinetic interactions. The effects of coadministration on AUC, C_{max}, and C_{min} values are summarized in Table 3 (effect of other drugs on amprenavir) and Table 5 (effect of LEXIVA on other drugs). In addition, since LEXIVA delivers comparable amprenavir plasma concentrations as AGENERASE, drug interaction data derived

from studies with AGENERASE are provided in Tables 4 and 6. For information regarding clinical recommendations, see PRECAUTIONS: Drug Interactions.

Table 3. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After Administration of LEXIVA in the Presence of the Coadministered Drug

Coadministered Drug(s) and Dose(s)	Dose of **LEXIVA***	n	% Change in **Amprenavir** Pharmacokinetic Parameters (90% CI)		
			C_{max}	AUC	C_{min}
Antacid (MAALOX TC®)	1,400 mg single dose	30	↓35 (↓24 to ↓42)	↓18 (↓9 to ↓26)	↑14 (↓7 to ↑39)
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↓18 (↓34 to ↑1)	↓27 (↓41 to ↓12)	↓12 (↓27 to ↑6)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	⇔	⇔	⇔
Efavirenz 600 mg q.d. for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	⇔	↓13 (↓30 to ↑7)	↓36 (↓8 to ↓56)
Efavirenz 600 mg q.d. plus additional Ritonavir 100 mg q.d for 2 weeks	1,400 mg q.d. plus ritonavir 200 mg q.d. for 2 weeks	16	↑18 (↑1 to ↑38)	↑11 (0 to ↑24)	⇔
Efavirenz 600 mg q.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	⇔	⇔	↓17 (↓4 to ↓29)
Lopinavir/ritonavir 533 mg/133 mg b.i.d.	1,400 mg b.i.d. for 2 weeks	18	See following section: **HIV Protease Inhibitors**		
Lopinavir/ritonavir 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↓58 (↓42 to ↓70)	↓63 (↓51 to ↓72)	↓65 (↓54 to ↓73)
Ranitidine 300 mg single dose	1,400 mg single dose	30	↓51 (↓43 to ↓58)	↓30 (↓22 to ↓37)	⇔ (↓19 to ↑21)

* Concomitant medication is also shown in this column where appropriate.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%).

Table 4. Drug Interactions: Pharmacokinetic Parameters for Amprenavir After Administration of AGENERASE in the Presence of the Coadministered Drug

Coadministered Drugs and Dose(s)	Dose of **AGENERASE***	n	% Change in **Amprenavir** Pharmacokinetic Parameters (90% CI)		
			C_{max}	AUC	C_{min}
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↑15 (↑1 to ↑31)	↑18 (↑8 to ↑29)	↑39 (↑31 to ↑47)
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↑40*	↑130*	↑125*
Ethinyl estradiol/norethindrone 0.035 mg/1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	⇔	↓22 (↓35 to ↓8)	↓20 (↓41 to ↑8)
Indinavir 800 mg t.i.d. for 2 weeks (fasted)	750 or 800 mg t.i.d. for 2 weeks (fasted)	9	↑18 (↓13 to ↑58)	↑33 (↑2 to ↑73)	↑25 (↓27 to ↑116)
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↓16 (↓25 to ↓6)	↑31 (↑20 to ↑42)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	⇔	⇔	NA
Nelfinavir 750 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	6	↓14 (↓38 to ↑20)	⇔	↑189 (↑52 to ↑448)
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	⇔	↓15 (↓28 to 0)	↓15 (↓38 to ↑17)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	↓70 (↓76 to ↓62)	↓82 (↓84 to ↓78)	↓92 (↓95 to ↓89)
Saquinavir 800 mg t.i.d. for 2 weeks (fed)	750 or 800 mg t.i.d. for 2 weeks (fed)	7	↓37 (↓54 to ↓14)	↓32 (↓49 to ↓9)	↓14 (↓52 to ↑54)
Zidovudine 300 mg single dose	600 mg single dose	12	⇔	↑13 (↓2 to ↑31)	NA

* Median percent change; confidence interval not reported.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study.

Table 5. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of LEXIVA

Coadministered Drugs and Dose(s)	Dose of **LEXIVA***	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI)		
			C_{max}	AUC	C_{min}
Atorvastatin 10 mg q.d. for 4 days	1,400 mg b.i.d. for 2 weeks	16	↑304 (↑205 to ↑437)	↑130 (↑100 to ↑164)	↓10 (↓27 to ↑12)
Atorvastatin 10 mg q.d. for 4 days	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	16	↑184 (↑126 to ↑257)	↑153 (↑115 to ↑199)	↑73 (↑45 to ↑108)
Lopinavir/ritonavir† 533 mg/133 mg b.i.d. for 2 weeks	1,400 mg b.i.d. for 2 weeks	18	See following section: **HIV Protease Inhibitors**		
Lopinavir/ritonavir† 400 mg/100 mg b.i.d. for 2 weeks	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 2 weeks	18	↑30 (↓15 to ↑47)	↑37 (↓20 to ↑55)	↑52 (↓28 to ↑82)

* Concomitant medication is also shown in this column where appropriate.

† Data represent lopinavir concentrations.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%).

Table 6. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of AGENERASE

Coadministered Drug(s) and Doses	Dose of **AGENERASE**	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI)		
			C_{max}	AUC	C_{min}
Clarithromycin 500 mg b.i.d. for 4 days	1,200 mg b.i.d. for 4 days	12	↓10 (↓24 to ↑7)	⇔	⇔
Delavirdine 600 mg b.i.d. for 10 days	600 mg b.i.d. for 10 days	9	↓47*	↓61*	↓88*
Ethinyl estradiol 0.035 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	⇔	⇔	↑32 (↓3 to ↑79)
Ketoconazole 400 mg single dose	1,200 mg single dose	12	↑19 (↑8 to ↑33)	↑44 (↑31 to ↑59)	NA
Lamivudine 150 mg single dose	600 mg single dose	11	⇔	⇔	NA
Methadone 44 to 100 mg q.d. for >30 days	1,200 mg b.i.d. for 10 days	16	R-Methadone (active)		
			↓25 (↓32 to ↓18)	↓13 (↓21 to ↓5)	↓21 (↓32 to ↓9)
			S-Methadone (inactive)		
			↓48 (↓55 to ↓40)	↓40 (↓46 to ↓32)	↓53 (↓60 to ↓43)
Norethindrone 1 mg for 1 cycle	1,200 mg b.i.d. for 28 days	10	⇔	↑18 ↑1 to ↑38	↑45 ↑13 to ↑88
Rifabutin 300 mg q.d. for 10 days	1,200 mg b.i.d. for 10 days	5	↑119 (↑82 to ↑164)	↑193 (↑156 to ↑235)	↑271 (↑171 to ↑409)
Rifampin 300 mg q.d. for 4 days	1,200 mg b.i.d. for 4 days	11	⇔	⇔	ND
Zidovudine 300 mg single dose	600 mg single dose	12	↑40 (↑14 to ↑71)	↑31 (↑19 to ↑45)	NA

* Median percent change; confidence interval not reported.

↑ = Increase; ↓ = Decrease; ⇔ = No change (↑ or ↓<10%); NA = C_{min} not calculated for single-dose study; ND = Interaction cannot be determined as C_{min} was below the lower limit of quantitation.

Nucleoside Reverse Transcriptase Inhibitors: There was no clinically significant effect of amprenavir after administration of AGENERASE on abacavir in subjects receiving both agents based on historical data.

In a phase III clinical trial (APV30003), plasma amprenavir trough concentrations were similar for subjects receiving tenofovir disoproxil fumarate in combination with LEXIVA and ritonavir as compared to subjects not receiving tenofovir.

HIV Protease Inhibitors: In a 3-arm, randomized, cross-over study involving healthy volunteers, amprenavir pharmacokinetics were compared after administration of LEXIVA 1,400 mg twice daily plus lopinavir/ritonavir 533 mg/133 mg twice daily for 2 weeks versus LEXIVA 700 mg twice daily plus ritonavir 100 mg twice daily for 2 weeks. Amprenavir concentrations were lower with the regimen containing lopinavir/ritonavir: C_{max} was 13% lower, AUC was 26% lower, and C_{min} was 42% lower. In the same study, lopinavir pharmacokinetics were compared after administration of LEXIVA 1,400 mg twice daily plus lopinavir/ritonavir 533 mg/133 mg twice daily for 2 weeks versus lopinavir/ritonavir 400 mg/100 mg twice daily for 2 weeks. Lopinavir concentrations were similar (less than 10% change in C_{max}, AUC, and C_{min} values) with these 2 regimens.

The effect of amprenavir after administration of AGENERASE on concentrations of other HIV protease inhibitors in subjects receiving both agents was evaluated using comparisons to historical data. Indinavir steady-state C_{max}, AUC, and C_{min} were decreased by 22%, 38%, and 27%, respectively, by concomitant amprenavir. Similar decreases in C_{max} and AUC were seen after the first dose. Saquinavir steady-state C_{max}, AUC, and C_{min} were increased 21%, decreased 19%, and decreased 48%, respectively, by concomitant amprenavir. Nelfinavir steady-state C_{max}, AUC, and C_{min} were increased by 12%, 15%, and 14%, respectively, by concomitant amprenavir.

Methadone: Coadministration of amprenavir and methadone can decrease plasma levels of methadone.

Coadministration of amprenavir and methadone as compared to a non-matched historical control group resulted in a 30%, 27%, and 25% decrease in serum amprenavir AUC, C_{max}, and C_{min}, respectively.

/S/

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Concurrence:

/S/

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6 Appendix

6.1 Individual Study Reviews (16)

APV10006

TITLE: A Pivotal, Phase I, Single-Dose, Open-Label, Randomized, Two-Way Crossover Study to Assess the Bioequivalence of 2×700mg GW433908 Oral Film-coated Tablets to 3×465mg GW433908 Oral Film-coated Tablets in Healthy Adult Subjects

BACKGROUND: This study assessed the bioequivalence of the 700mg (variant A) GW433908 oral film-coated tablet formulation to the 465mg (variant A) GW433908 oral film-coated tablet formulation following administration of single oral GW433908 doses in healthy adult subjects. Both the 465mg and the 700mg oral film-coated tablet formulations were used in Phase III GW433908 trials and the 700mg formulation is expected to be the market formulation.

OBJECTIVES: The primary study objective was to assess the single-dose bioequivalence of 2x700mg GW433908 oral film-coated tablets to 3x465mg GW433908 oral film-coated tablets in healthy adult subjects.

SUBJECTS AND STUDY DESIGN: Protocol APV10006 was a phase I, single-dose, open-label, randomized, two-way crossover study conducted in 32 healthy adult subjects at a single study center. Subjects were randomized to one of the following treatment sequences:

Treatment Sequence	Sample Size	Period 1	Period 2
1	16	Treatment 1	Treatment 2
2	16	Treatment 2	Treatment 1
Treatment 1 = 465mg GW433908 oral film-coated tablet[a] fasted Treatment 2 = 700mg GW433908 oral film-coated tablet[b] fasted			

a. GW433908 administered as 3×465mg (400mg amprenavir molar equivalents) oral film-coated tablets
b. GW433908 administered as 2×700mg (600mg amprenavir molar equivalents) oral film-coated tablets

Subjects underwent a washout period of 4-7 days between treatments.

Thirty-three subjects were enrolled and thirty-two of these 33 subjects completed the study. The demographic characteristics of these were as following: Male (67%) and female (33%); White (91%), Asian (6%) and Hispanic (3%).

INVESTIGATOR AND STUDY LOCATION: [redacted] Glaxo Wellcome Medicines Research Unit, Prince of Wales Hospital, Australia

FORMULATION:

Study Drug/Dose	Batch Number	Expiration/Review Date
465mg tablet GW433908	E00B4	31 January 2001
700mg tablet GW433908	E00B149	28 February 2001

SAMPLE COLLECTION: Blood samples for measurement of APV concentrations were collected prior to the dose (0 hour) and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours after dose administration in each of the two periods.

ASSAY: Plasma samples were analysed for amprenavir concentrations by a validated ——— method at — GlaxoWellcome, RTP, USA. The quality control samples had coefficients of variation less than or equal to — 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, Tmax 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 PK Parameters (N=32)

	3X465 mg Tablet	2X700 mg Tablet
C_{max} (µg/mL)	6.17 ± 2.36	6.00 ± 2.54
Geometric mean	5.74	5.50
AUC_{inf} (µg-hr/mL)	26.90 ± 11.53	26.56 ± 11.74
Geometric mean	24.70	24.32
T_{max} (h)	1.72 ± 1.01	1.86 ± 1.05

Table 2. Relative Bioavailability of the GW433908 Tablet Formulations

Bioequivalence Assessment of GW433908 Tablet Formulations APV10006 (N=32)			
	Geometric LS Mean		Ratio (90% CI)
Plasma Amprenavir Pharmacokinetic Parameter	3x465mg film-coated tablets	2x700mg film-coated tablets	3x465mg tablets/ 2x700mg tablets
AUC_∞ (µg.h/mL)	24.61	24.12	0.98 (0.93-1.03)
C_{max} (µg/mL)	5.71	5.47	0.96 (0.86-1.07)

SAFETY RESULTS: There were no deaths, serious adverse events, or other significant adverse events reported during the study.

CONCLUSIONS AND DISCUSSION: 1395mg of the GW433908 465mg oral film-coated tablet formulation and 1400mg of the GW433908 700mg oral film-coated tablet formulation were bioequivalent when administered to healthy adult subjects.

APV10007

TITLE: A Phase I, Single-Dose, Open-Label, Randomized, Three-Way, Balanced, Crossover Study to Assess the Effect of MAALOX TC and ZANTAC on Plasma Amprenavir Pharmacokinetics Following Administration of a 1400mg Single Dose of GW433908

BACKGROUND: Although no interaction with antacids is known, the chemical properties of GW433908 and APV make an interaction with antacids theoretically possible. First, GW433908 and APV are more soluble at acidic pH. Second, binding of metal cations, present in acid neutralizing agents, to the phosphate group on GW433908 potentially could alter solubility or prevent presystemic conversion of the prodrug to APV. This study assessed the effect of antacids on the single-dose PK of APV and GW433908. The acid neutralizer and phosphate binder MAALOX TC and the H2-antagonist ZANTAC were administered separately with GW433908 to elucidate whether phosphate binding or change in pH may underlie any drug interaction mechanism.

OBJECTIVES: The primary objectives were to assess the effect of MAALOX TC 30mL (1800mg magnesium hydroxide and 3600mg aluminum hydroxide dried gel USP (equivalent to 2754 mg aluminum hydroxide)) on plasma APV PK when coadministered with a single dose of GW433908 1400mg and to assess the effect of ZANTAC 300mg on plasma APV PK when administered one hour prior to a single dose of GW433908 1400mg. The secondary objectives were to assess the effect of MAALOX TC 30mL on plasma GW433908 PK when coadministered with a single dose of GW433908 1400mg, to assess the effect of ZANTAC 300mg on plasma GW433908 PK when administered one hour prior to a single dose of GW433908 1400mg and to assess the safety and tolerability of a single dose of GW433908 1400mg in combination with MAALOX TC 30mL or ZANTAC in healthy adult subjects.

SUBJECTS AND STUDY DESIGN:

Treatment Sequence	Sample Size	Period 1	Period 2	Period 3
A	5	Treatment 1	Treatment 2	Treatment 3
B	5	Treatment 1	Treatment 3	Treatment 2
C	5	Treatment 2	Treatment 1	Treatment 3
D	5	Treatment 2	Treatment 3	Treatment 1
E	5	Treatment 3	Treatment 1	Treatment 2
F	5	Treatment 3	Treatment 2	Treatment 1
Treatment 1 = GW433908 1400mg[a] Treatment 2 = GW433908 1400mg[a] administered immediately following **MAALOX TC** 30mL[b] Treatment 3 = GW433908 1400mg[a] one hour after a single dose of **ZANTAC** 300mg				

a Given as two GW433908 oral film-coated 700mg tablets (600mg APV molar equivalents)

b Given as 30mL of **MAALOX TC** (1800 mg magnesium hydroxide and 3600mg aluminum hydroxide dried gel USP (equivalent to 2754 mg aluminum hydroxide)

There was a washout period of 4 to 7 days between doses. All treatments were administered after an overnight fast to ensure low gastric pH. Water was allowed ad libitum during the fast. Subjects continued to fast for at least 4 hours post-GW433908 administration. Water was allowed ad libitum two hours post-dose. Regular meals were served approximately 4 and 10 hours post-dose.

Thirty subjects were enrolled and twenty-six of these 30 subjects completed the study. The demographic characteristics of these were as following: Male (92%) and female (8%); White (69%), Black (27%) and Asian (4%).

INVESTIGATOR AND STUDY LOCATION: [redacted]

FORMULATION: GW433908 700mg tablet (E01B151), ZANTAC 300mg tablet, MAALOX TC 30 mL

SAMPLE COLLECTION: Blood samples for measurement of APV and GW433908 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 post dose.

ASSAY: Plasma PK samples were analyzed for APV and GW433908 by the bioanalysis section of GSK Drug Metabolism and Pharmacokinetics, 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], respectively for GW433908 and APV.

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_{last}, Cmax and C_{12} 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, Geometric Mean (95% CI)

Plasma APV PK Parameter	Treatment 1 N=26	Treatment 2 N=26	Treatment 3 N=26
AUC_{last} (µg*h/mL)	20.67 (17.31-24.69)	16.98 (14.32-20.14)	14.45 (11.46-18.22)
AUC_{∞} [a] (µg*h/mL)	22.05 (18.50-26.30)	18.71 (15.72-22.26)	16.03 (12.55-20.48)
C_{max} (µg/mL)	4.73 (4.11-5.45)	3.09 (2.69-3.54)	2.31 (1.86-2.87)
t_{max} [b] (h)	1.50 (0.75-5.00)	1.50 (0.75-5.00)	1.75 (0.75-5.00)
C_{12} (µg/mL)	0.32 (0.25-0.40)	0.36 (0.28-0.48)	0.32 (0.24-0.42)

Treatment 1 = GW433908 1400mg
Treatment 2 = GW433908 1400mg immediately following **MAALOX TC** 30mL
Treatment 3 = GW433908 1400mg one hour after a single dose of **ZANTAC** 300mg tablet

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

Plasma APV PK Parameter	Treatment 2/Treatment 1 N=26	Treatment 3/Treatment 1 N=26
AUC_{last} (µg*h/mL)	0.82 (0.74-0.91)	0.70 (0.63-0.78)
AUC_{∞} [a] (µg*h/mL)	0.85 (0.77-0.94)	0.74 (0.66-0.82)
C_{max} (µg/mL)	0.65 (0.57-0.76)	0.49 (0.42-0.57)
t_{max} [b] (h)	1.18 (0.84-1.52)	1.37 (1.03-1.71)
C_{12} (µg/mL)	1.14 (0.93-1.39)	0.99 (0.81-1.21)
Treatment 1 = GW433908 1400mg Treatment 2 = GW433908 1400mg immediately following **MAALOX TC** 30mL Treatment 3 = GW433908 1400mg one hour after a single dose of **ZANTAC** 300mg tablet		

a N=24 for AUC_{∞}

b t_{max} data presented as LS mean ratio (90% CI)

PK analysis of plasma GW433908 concentration-time data was not done because GW433908 was quantifiable at very few time points in the subjects. 22 (85%) had quantifiable GW433908 concentrations after receiving Treatment 1 (GW433908), 10 (38%) after receiving Treatment 3 (GW433908 + ZANTAC), and only 1 subject (<4%) had quantifiable GW433908 concentrations after receiving Treatment 2 (GW433908 + MAALOX TC).

SAFETY RESULTS: The most commonly reported AEs were proteinuria (13%) and headache (10%). All other AEs occurred at a frequency of less than 10%. Consistent differences in AE frequencies between treatments were not observed. No serious adverse events or deaths were reported during this study.

CONCLUSIONS AND DISCUSSIONS: The study design is acceptable. Coadministration of MAALOX TC 30mL and GW433908 1400mg decreased plasma APV AUC_{last} by 18% and C_{max} by 35%. Coadministration of ZANTAC 300mg and GW433908 1400mg decreased plasma APV AUC_{last} by 30% and C_{max} by 51%.

The clinical relevance of this drug-drug interaction is not known. However, the sponsor thought that it should not be of clinical concern based on the following arguments. In Study PROA2002 (> 48 weeks), three AGENERASE regimens, 900mg BID, 1050mg BID, and 1200mg BID, resulted in similar efficacy. The comparable efficacy of the 900mg BID regimen given the reduced plasma APV exposure of ~35% suggests that a reduction in plasma APV $AUC_{\tau,ss}$ of ~35% does not compromise the efficacy of AGENERASE. The changes in plasma APV PK parameters observed with coadministration of GW433908 with MAALOX TC or ZANTAC both were within the ≤35% decrease. In addition, there was either a minor (14%) increase or no change in plasma APV C_{12} values when GW433908 was coadministered with MAALOX TC or ZANTAC, respectively.

The mechanism of the interaction between GW433908 and antacid medications (including $histamine_2$ receptor antagonists and acid neutralizers) was likely due to changes in gastric pH and phosphate binding that could affect GW433908 solubility and subsequent plasma APV pharmacokinetics.

We will recommend adding this drug-drug interaction information to Table 13. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen may be Recommended Based on Drug Interaction Studies or Predicted Interaction. Also, the results of this study suggest that co-administration with proton pump inhibitor may lead to decreased amprenavir exposure.

APV10008

TITLE: A Phase I, Single-Dose, Open-Label, Randomized, Four-Period, Balanced Crossover Study to Assess the Relative Bioavailability of the GW433908 Oral Suspension Relative to the GW433908 Oral Film-coated 700mg Tablet and to Assess the Effects of Food on Amprenavir Pharmacokinetics Following Administration of these Formulations to Healthy Adult Subjects

BACKGROUND: This study assessed the single-dose relative bioavailability of the GW433908 oral suspension formulation and the GW433908 oral film-coated 700mg variant A tablet formulation used in clinical trials. The effects of food on single-dose APV PK following administration of the GW433908 oral suspension and also following administration of the GW433908 oral film-coated 700mg tablet formulation to healthy adult subjects were also assessed. The results of this study were used [redacted] and to optimize dosing conditions with respect to food.

Subsequent changes in the drug substance manufacturing process occurred and GW433908 oral tablets and suspension formulations using this revised process will be supplied to the market. Thus, this study, APV10008, was no longer considered a pivotal study and a subsequent pivotal study, APV10016, linking the GW433908 oral tablet and suspension market formulations was conducted.

OBJECTIVES: The primary objectives were to to assess the single-dose relative bioavailability of the GW433908 oral suspension formulation and the GW433908 oral film-coated 700mg tablet formulation, to assess the effects of food on single-dose amprenavir pharmacokinetics following administration of the GW433908 oral suspension formulation, and to assess the effects of food on single-dose amprenavir pharmacokinetics following administration of the GW433908 oral film-coated 700mg tablet formulation.

SUBJECTS AND STUDY DESIGN:

Sequence	Sample Size	Period 1	Period 2	Period 3	Period 4
1	9	Treatment A	Treatment D	Treatment B	Treatment C
2	9	Treatment B	Treatment A	Treatment C	Treatment D
3	9	Treatment C	Treatment B	Treatment D	Treatment A
4	9	Treatment D	Treatment C	Treatment A	Treatment B

Treatment A = 2 GW433908 oral film-coated 700mg tablets[a] administered fasted.
Treatment B = 2 GW433908 oral film-coated 700mg tablets[a] administered following a meal.
Treatment C = 28mL of the 50mg/mL GW433908 oral suspension[b] administered fasted
Treatment D = 28mL of the 50mg/mL GW433908 oral suspension[b] administered following a meal.

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

There was a washout period of 4 to 7 days between each dose. For the fasted treatments (Treatments A and C): Subjects were required to fast 10 hours before administration of study drug. Water was permitted during the fast, except for 1 hour prior to dosing. Subjects fasted for an additional 4h after dosing. Water was permitted beginning 2 hours after dosing. Scheduled standard meals were served at approximately 4 and 10 hours post-dose. For the fed treatments (Treatments B and D): Subjects were required to fast 10h before administration of a standard test meal. Water was permitted during the fast, except for 1h prior to dosing. Each subject was served a standard test meal and ingested this meal within 30 minutes. Study drug was administered with 240mL (8oz) of water immediately (within 5 minutes) after completion of the meal. Additional water was permitted as soon as 2 hours after dosing. Scheduled standard meals were served at approximately 4 and 10 hours post-dose. The standard test meal was the representative example given by the US Food and Drug Administration (FDA). This standard test meal has high fat (approximately 50% of the caloric content of the meal) and high calories (approximately 1000 calories).

Thirty-nine subjects were enrolled and thirty-one of these 39 subjects completed the study. The demographic characteristics of these were as following: Male (79%) and female (21%); White (41%), Black (49) and other (10%).

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

FORMULATION:

Study Drug	Batch Number	Expiry Date
Tablet, 700mg	E00B149	31 August 2001
Oral Suspension, 50mg/mL	C01L426	16 October 2001

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 on each of the four periods.

ASSAY: Plasma PK samples were analyzed for APV by [redacted] he 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 treatments.

PHARMACOKINETIC RESULTS:

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

	Tablet Fasted Treatment A (N=31)	Tablet Fed Treatment B (N=31)	Suspension Fasted Treatment C (N=31)	Suspension Fed Treatment D (N=31)
AUC_{∞} (µg.h/mL)				
Geometric Mean	19.05	19.37	21.99	15.24
95% CI	(16.34, 22.20)	(16.97, 22.11)	(18.83, 25.67)	(12.70, 18.29)
C_{max} (µg/mL)				
Geometric Mean	4.26	4.51	5.54	2.83
95% CI	(3.69, 4.92)	(3.83, 5.30)	(4.81, 6.38)	(2.35, 3.41)
t_{max} (h)				
Median	1.5	2.0	1.0	2.5
Range	(0.7-5.0)	(0.7-6.0)	(0.7-3.0)	(0.5-4.0)
t_{lag} (h)				
Median	0.22	0.25	0.00	0.00
Range	(0.00 – 0.50)	(0.00 – 1.00)	(0.00 – 0.00)	(0.00 – 0.73)

Table 2. Summary of Fasted Suspension/Tablet Relative Bioavailability

	Geometric LS Mean		Ratio (90% CI)
Plasma APV PK Parameter	Tablet Fasted (Treatment A)	Suspension Fasted (Treatment C)	C/A
AUC_{∞} (µg.h/ml)	19.0	22.1	1.16 (1.06-1.27)
C_{max} (µg/ml)	4.25	5.55	1.31 (1.16-1.47)

Table 3. Summary of Tablet Food Effect Analysis

	Geometric LS Mean		Ratio (90% CI)
Plasma APV PK Parameter	Tablet Fasted (Treatment A)	Tablet Fed (Treatment B)	B/A
AUC_{∞} (µg.h/ml)	19.0	19.4	1.02 (0.93-1.12)
C_{max} (µg/ml)	4.25	4.50	1.06 (0.94-1.19)

Table 4. Summary of Suspension Food Effect Analysis (N=32)

	Geometric LS Mean		Ratio (90% CI)
Plasma APV PK Parameter	Suspension Fasted (Treatment C)	Suspension Fed (Treatment D)	D/C
AUC_{∞} (µg.h/ml)	22.1	15.3	0.69 (0.63-0.76)
C_{max} (µg/ml)	5.55	2.84	0.51 (0.45-0.57)

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

CONCLUSIONS AND DISCUSSION: In the fasting state, the GW433908 oral suspension delivered a 16% higher AUC (GLS mean ratio: 1.16; 90% CI: 1.06 - 1.27) and a 31% higher Cmax (GLS mean ratio: 1.31; 90% CI: 1.16 - 1.47) as compared to the GW433908 oral tablet. Administration of the GW433908 oral tablet with a high-fat breakfast resulted in equivalent plasma APV AUC and Cmax values as compared to the GW433908 oral tablet administered under fasting conditions. Administration of the GW433908 oral suspension formulation with a standard high-fat breakfast significantly decreased plasma APV AUC and Cmax values by 31% and 49%, respectively, as compared to the GW433908 oral suspension formulation administered under fasting conditions.

In the NDA 21548, 700 mg tablet variant A is the only intended market formulation. Based on the study result, fosamprenavir tablets may be administered without regard to food intake.

APV10009

TITLE: A Phase I, Randomized Study to Assess the Effect of Efavirenz 600mg QD on Steady-State Plasma Total Amprenavir and Ritonavir PK Following Coadministration with GW433908 1395mg QD + Ritonavir 200mg QD or GW433908 1395mg QD + Ritonavir 300mg QD for 14 Days as Compared to GW433908 1395mg QD + Ritonavir 200mg QD for 14 Days in Healthy Adult Subjects

BACKGROUND: A National Institutes of Health (NIH) sponsored study demonstrated that EFV decreased plasma APV AUC, Cmax, and Cmin by 24%, 33%, and 43%, respectively, in eight HIV-infected subjects who received APV 1200mg twice daily (BID) with and without EFV 600mg once daily (QD). Another NIH-sponsored study demonstrated that a RTV dosage regimen of at least 200mg BID was sufficient to counteract the CYP3A4 induction effect of EFV such that APV concentrations were not different when APV 1200mg BID was coadministered with RTV with or without EFV 600mg QD in HIV-infected subjects. Data from two small studies indicate that administration of APV 600mg BID + RTV 100mg BID + EFV 600mg QD results in plasma APV concentrations higher than those achieved with the standard APV 1200mg BID (without RTV) regimen, though data indicate that 100mg of RTV is not sufficient to completely counteract the CYP3A4 induction effect of EFV. When EFV 600mg QD and RTV 500mg BID were coadministered, plasma RTV and EFV AUC values were both increased by ~ 20%. No definitive PK data were available to aid in dose selection when APV or GW433908 are coadministered with RTV and EFV QD. Therefore, the present study assessed the effect of EFV 600mg QD on steady-state plasma APV PK following coadministration with GW433908 1395mg QD + RTV 200mg QD or GW433908 1395mg QD + RTV 300mg QD as compared to GW433908 1395mg QD + RTV 200mg QD (without EFV) in healthy adult subjects. These data will facilitate GW433908 and RTV dose selection for a subsequent Phase III GW433908 study in PI-experienced subjects.

OBJECTIVES: The primary objectives were to compare plasma APV PK following administration of GW433908 1395mg QD + RTV 200mg QD + EFV 600mg QD for 14 days versus GW433908 1395mg QD + RTV 200mg QD for 14 days and to compare plasma APV PK following administration of GW433908 1395mg QD + RTV 300mg QD + EFV 600mg QD for 14 days versus GW433908 1395mg QD + RTV 200mg QD for 14 days. Secondary objectives were to compare GW433908 and RTV PK for the same regimens mentioned for the primary objectives, to assess plasma unbound APV concentrations, to assess plasma APV and RTV concentrations 48 hours after coadministration of GW433908 + RTV + EFV for 14 days, and to assess the safety and tolerability of the three regimens.

SUBJECTS AND STUDY DESIGN: This was a Phase I, open-label, randomized, two-arm, two-period study conducted in healthy adult subjects at three study centers in the US. Thirty-two subjects were to be randomized into one of two arms as outlined in the following table in order to obtain 24 evaluable subjects (12 subjects per arm).

Arm	Sample Size	Period 1 (Days 1-14)	Period 2 (Days 15-28)
1	16	Treatment A	Treatment B
2	16	Treatment A	Treatment C
Treatment A = GW433908 1395mg QD + RTV 200mg QD Treatment B = GW433908 1395mg QD + RTV 200mg QD + EFV 600mg QD Treatment C = GW433908 1395mg QD + RTV 300mg QD + EFV 600mg QD			

GW433908 1395mg = 1200mg APV molar equivalents

Thirty-two subjects were enrolled and twenty-two of these 32 subjects completed the study (11 in Arm 1 and 11 in Arm 2). The overall demographic characteristics of these were as following: Male (84%) and female (16%); White (72%), Black (22%).

GW433908 and RTV were administered in the morning without regard to meals. EFV was administered in the evening at least 2 hours apart from a meal. On the evenings of Days 13 and 27, subjects were admitted to the study center overnight in preparation for PK assessments on the following day(s). The evening dose of EFV was administered at least 2 hours apart from a meal on Day 27. Subjects fasted for 10 hours prior to administration of the last morning dose of study drug (GW433908 and RTV) on Days 14 and 28. Water was allowed during the 10 hour fast. Subjects fasted for an additional 4 hours after administration of study drug. Regular scheduled lunch and supper was provided to the subjects approximately 4 and 10 hours, respectively, after administration of study drug.

INVESTIGATOR AND STUDY LOCATION:

FORMULATION: GW433908 465mg tablet (E00B4 and E00B173), Ritonavir 100 mg soft gelatin capsule, Efavirenz 200mg capsule.

SAMPLE COLLECTION: Blood samples for measurement of plasma APV, GW433908, and RTV concentrations were collected over 24 hours at 0, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 10, 12, 16, and 24 hours on Days 14-15 of Period 1, and Days 28-29 of Period 2. An additional whole blood sample for measurement of steady state plasma unbound APV concentrations was collected at 24 hours post-dose on Days 15 and 29.

ASSAY: Plasma PK samples were analyzed for APV and GW433908 by the bioanalysis section of GSK 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 GW443908, APV and ritonavir.

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 A Day 14 N=22	Treatment B Day 28 N=11	Treatment C Day 28 N=11
$AUC_{\tau,ss}$ (µg.h/mL)	69.4 (59.7-80.8)	66.4 (51.2-86.0)	70.1 (52.7-93.2)
$C_{max,ss}$ (µg/mL)	7.24 (6.32-8.28)	8.10 (6.51-10.07)	7.78 (6.22-9.75)
$C_{\tau,ss}$ (µg/mL)	1.45 (1.16-1.81)	1.00 (0.61-1.64)	1.46 (0.94-2.26)
$t_{max,ss}$ (h)[a]	2.1 (0.8-5.0)	1.5 (0.8-5.0)	1.5 (0.8-5.0)

a $t_{max,ss}$ data presented as median (range)
Treatment A = GW433908 1395mg QD + RTV 200mg QD
Treatment B = GW433908 1395mg QD + RTV 200mg QD + EFV 600mg QD
Treatment C = GW433908 1395mg QD + RTV 300mg QD + EFV 600mg QD

Table 2. Steady-State Plasma RTV PK Parameter Estimates, Geometric Mean (95% CI)

Plasma RTV PK Parameter	Treatment A Day 14 N=22	Treatment B Day 28 N=11	Treatment C Day 28 N=11
$AUC_{\tau,ss}$ (µg.h/mL)	9.69 (7.74-12.12)	7.56 (4.42-12.93)	18.76 (13.74-25.61)
$C_{max,ss}$ (µg/mL)	1.85 (1.45-2.35)	1.66 (0.93-2.95)	3.58 (2.43-5.27)
$C_{\tau,ss}$ (µg/mL)	0.04 (0.03-0.0.06)	0.03 (0.01-0.05)	0.09 (0.04-0.19)
$t_{max,ss}$ (h)[a]	2.8 (1.5-5.0)	2.5 (1.5-4.0)	3.0 (1.0-8.0)

a $t_{max,ss}$ data presented as median (range)
Treatment A = GW433908 1395mg QD + RTV 200mg QD
Treatment B = GW433908 1395mg QD + RTV 200mg QD + EFV 600mg QD
Treatment C = GW433908 1395mg QD + RTV 300mg QD + EFV 600mg QD

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Table 3. Steady-State Plasma GW433908 PK Parameter Estimates, Geometric Mean (95% CI)

Plasma GW433908 PK Parameter	Treatment A Day 14 N=15[a]	Treatment B Day 28 N=9[a]	Treatment C Day 28 N=8[a]
$AUC_{last,ss}$ (µg.h/mL)	0.006 (0.003-0.013)	0.015 (0.004-0.051)	0.008 (0.003-0.023)
$C_{max,ss}$ (µg/mL)	0.011 (0.008-0.016)	0.017 (0.006-0.051)	0.012 (0.008-0.019)
$t_{max,ss}$ (h)[b]	1.5 (0.5-3.0)	1.5 (0.8-4.0)	1.3 (0.5-2.5)

a Only subjects with quantifiable GW433908 concentrations were included in the descriptive statistics of plasma GW433908 PK; N=15 of 22 for Treatment A, N=9 of 11 for Treatment B, N=8 of 11 for Treatment C.

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

Treatment A = GW433908 1395mg QD + RTV 200mg QD
Treatment B = GW433908 1395mg QD + RTV 200mg QD + EFV 600mg QD
Treatment C = GW433908 1395mg QD + RTV 300mg QD + EFV 600mg QD

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

Plasma APV PK Parameter	Arm 1 Treatment B/Treatment A N=11	Arm 2 Treatment C/Treatment A N=11
$AUC_{\tau,ss}$ (µg.h/mL)	0.87 (0.70-1.07)	1.11 (1.00-1.24)
$C_{max,ss}$ (µg/mL)	1.02 (0.83-1.25)	1.18 (1.01-1.38)
$C_{\tau,ss}$ (µg/mL)	0.64 (0.44-0.92)	1.09 (0.88-1.36)
$t_{max,ss}$ (h)[a]	0.60 (0.33-0.87)	0.92 (0.58-1.25)

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

Treatment A = GW433908 1395mg QD + RTV 200mg QD
Treatment B = GW433908 1395mg QD + RTV 200mg QD + EFV 600mg QD
Treatment C = GW433908 1395mg QD + RTV 300mg QD + EFV 600mg QD

SAFETY RESULTS: Most of the AEs were mild or moderate; two severe AEs (One subject had severe nausea with moderate vomiting and the other subject had severe rash) were reported. AEs were reported with similar frequency between the two periods and among the three treatments, with the exception of dizziness, which appeared to be more frequently reported by subjects in Period 2 when EFV was coadministered with GW433908 and RTV.

CONCLUSIONS AND DISCUSSIONS: The study design is acceptable. Coadministration of EFV 600mg QD with GW433908 1395mg QD and RTV 200mg QD decreased plasma APV exposure ($C\tau$ decreased by 36% and $AUC\tau$ decreased by 13%). The addition of an extra 100mg of RTV (i.e. RTV 300mg QD) to the combination of GW433908 1395mg QD and EFV 600mg QD maintained plasma APV concentrations comparable to those achieved with GW433908 1395mg QD + RTV 200mg QD (without EFV); Geometric LS mean ratio (90% CI) for $AUC\tau$: 1.11(1.00-1.24), Cmax: 1.18 (1.01-1.38), $C\tau$: 1.09 (0.88-1.36). Plasma RTV exposures were increased for RTV 300mg QD versus RTV 200mg QD.

The results of this study indicate that RTV 200mg QD partially blocks and RTV 300mg QD completely blocks the induction of APV metabolism by EFV when coadministered with GW433908 1395mg QD and EFV 600mg QD, without obvious differences in safety and tolerability between the two regimens.

We will recommend co-administration of RTV 300 mg QD when EFV 600mg QD is administered with GW433908 1400mg QD.

APV10010

TITLE: A Phase I, Randomized Study to Assess the Effect of Efavirenz 600mg QD on Steady-State Plasma Total Amprenavir Pharmacokinetics Following Co-administration with GW433908 700mg BID + Ritonavir 100mg BID or GW433908 700mg BID + Ritonavir 200mg BID for 14 days as Compared to GW433908 700mg BID + RTV 100mg BID for 14 Days in Healthy Adult Subjects

BACKGROUND: APV10010 was designed to adequately assess, in a fully powered within-subject comparative study, the effect of EFV 600mg QD on steady-state plasma total APV PK following co-administration with GW433908 700mg BID + RTV 100mg BID or GW433908 700mg BID + RTV 200mg BID as compared to GW433908 700mg BID + RTV 100mg BID (without EFV) in healthy adult subjects.

OBJECTIVES: The primary objectives were to compare plasma APV PK following administration of GW433908 700mg BID +RTV 100mg BID + EFV 600mg QD for 14 days versus GW433908 700mg BID + RTV 100mg BID for 14 days and to compare plasma APV PK following administration of GW433908 700mg BID + RTV 200mg BID + EFV 600mg QD for 14 days versus GW433908 700mg BID + RTV 100mg BID for 14 days.

SUBJECTS AND STUDY DESIGN: Protocol APV10010 was a Phase I, open-label, randomized, two-arm, two-period study conducted in healthy adult subjects at three study centers in the US. Thirty-two subjects were to be randomized to one of the following arms:

Thirty-one subjects were enrolled and twenty-four of these 31 subjects completed the study (14 in Arm 1 and 10 in Arm 2). The overall demographic characteristics of these were as following: Male (81%) and female (19%); White (77%), Black (23%).

Arm	Sample Size	Period 1 Days 1–14 (morning)	Period 2 Days 14 (evening) – 28 (morning)
1	16	Treatment A	Treatment B
2	16	Treatment A	Treatment C
Treatment A = GW433908[a] 700mg BID + RTV 100mg BID Treatment B = GW433908[a] 700mg BID + RTV 100mg BID + EFV 600mg QD Treatment C = GW433908[a] 700 mg BID + RTV 200 mg BID + EFV 600mg QD			

a GW433908 700mg = 600mg APV molar equivalents

GW433908 and RTV were administered in the morning and in the evening with approximately 12 hours between doses, without regard to meals. EFV was administered in the evening at least 2 hours apart from a meal. On the evenings of Days 13 and 27, subjects were admitted to the study center overnight in preparation for PK assessments the following day(s). One plasma sample was collected on each of these days within 10-14 hours following a GW433908 + RTV dose (the GW433908 + RTV dose administered on the morning of Days 13 and 27) for measurement of plasma APV trough concentrations. These PK samples were collected prior to administration of the evening dose of study drugs. The last dose of EFV was administered at least 2 hours apart from a meal on the evening of Day 27. Subjects fasted for 10 hours prior to administration of the last dose of each period's study drug (GW433908 + RTV) on the mornings of Days 14 and 28. Water was allowed during the 10-hour fast. Subjects fasted for an additional 4 hours after administration of the last dose of each period's study drug and water was permitted 2 hours after administration of the last dose of each period's study drug.

INVESTIGATOR AND STUDY LOCATION: '

FORMULATION: GW433908 700mg tablet (E00B149), Ritonavir 100 mg soft gelatin capsule, Efavirenz 200mg capsule.

SAMPLE COLLECTION: Blood samples for measurement of plasma APV and RTV concentrations were collected over 12 hours at 0, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 10 and 12 hours on Days 14 and 28. An additional blood sample was collected at 24 hours post-dose on Day 29.

ASSAY: Plasma PK samples were analyzed for APV and GW433908 by the bioanalysis section of GSK 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 GW443908, APV and ritonavir.

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 A Day 14 N=24	Treatment B Day 28 N=14	Treatment C Day 28 N=10
$AUC_{\tau,ss}$ (µg.h/mL)	39.6 (34.5-45.3)	37.0 (31.4-43.7)	36.2 (29.1-44.9)
$C_{max,ss}$ (µg/mL)	6.08 (5.38-6.86)	6.11 (5.18-7.21)	5.49 (4.81-6.26)
$C_{\tau,ss}$ (µg/mL)	2.12 (1.77-2.54)	1.96 (1.62-2.38)	1.93 (1.45-2.57)
$t_{max,ss}$ (h)[a]	1.50 (0.75-5.00)	1.50 (0.73-2.50)	1.99 (0.75-5.07)

a $t_{max,ss}$ data presented as median (range)
Treatment A = GW433908 700mg BID + RTV 100mg BID
Treatment B = GW433908 700mg BID + RTV 100mg BID + EFV 600mg QD
Treatment C = GW433908 700mg BID + RTV 200mg BID + EFV 600mg QD

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Table 2. Steady-State Plasma RTV PK Parameter Estimates, Geometric Mean (95% CI)

Plasma RTV PK Parameter	Treatment A Day 14 N=24	Treatment B Day 28 N=14	Treatment C Day 28 N=10
$AUC_{\tau,ss}$ (µg.h/mL)	5.75 (4.75-6.96)	7.14 (4.92-10.35)	18.2 (13.55-24.35)
$C_{max,ss}$ (µg/mL)	1.20 (0.98-1.48)	1.36 (1.08-1.73)	3.60 (2.76-4.70)
$C_{\tau,ss}$ (µg/mL)	0.15 (0.11-0.22)	0.23 (0.12-0.45)	0.57 (0.31-1.06)
$t_{max,ss}$ (h)[a]	2.50 (1.00-5.00)	1.50 (0.75-3.00)	2.25 (1.50-10.00)

a $t_{max,ss}$ data presented as median (range)
Treatment A = GW433908 700mg BID + RTV 100mg BID
Treatment B = GW433908 700mg BID + RTV 100mg BID + EFV 600mg QD
Treatment C = GW433908 700mg BID + RTV 200mg BID + EFV 600mg QD

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

Plasma APV PK Parameter	Arm 1 Treatment B/Treatment A N=14	Arm 2 Treatment C/Treatment A N=10
$AUC_{\tau,ss}$ (µg.h/mL)	0.91 (0.80-1.03)	0.95 (0.87-1.04)
$C_{max,ss}$ (µg/mL)	0.98 (0.87-1.11)	0.93 (0.82-1.06)
$C_{\tau,ss}$ (µg/mL)	0.83 (0.71-0.96)	1.07 (0.96-1.19)
$t_{max,ss}$ (h)[a]	0.79 (0.48-1.10)	1.08 (0.64-1.52)

a LS mean ratio (90% CI) for $t_{max,ss}$
Treatment A = GW433908 700mg BID + RTV 100mg BID
Treatment B = GW433908 700mg BID + RTV 100mg BID + EFV 600mg QD
Treatment C = GW433908 700mg BID + RTV 200mg BID + EFV 600mg QD

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

CONCLUSIONS AND DISCUSSIONS: The study design is acceptable. Plasma APV concentrations were maintained when EFV 600 mg QD was coadministered with GW433908 700 mg BID + RTV 100 mg BID. The addition of an extra 100 mg of RTV (i.e. RTV 200 mg BID) did not provide a significant additional increase in plasma APV concentrations though trough point estimate increased from 0.83 to 1.07.

We recommend that no additional RTV dose is needed when GW433908 700mg BID + Ritonavir 100mg BID is co-administered with Efavirenz 600mg QD.

APV10011

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 533mg/Ritonavir 133mg BID + GW433908 1400mg BID, GW433908 700mg BID + Ritonavir 100mg BID, or Lopinavir 400mg/Ritonavir 100mg 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. The current study evaluated whether higher doses of both GW433908 and LPV/RTV in combination delivered similar plasma APV and LPV exposure as observed with each standard regimen of GW433908 + RTV and LPV/RTV. These data were intended to facilitate GW433908 and RTV dose selection when dosed with KALETRA for potential Phase III studies in PI experienced patients.

OBJECTIVES: The primary objectives were to compare plasma APV PK following administration of GW433908 1400mg BID + LPV 533mg/RTV 133mg BID for 14 days versus GW433908 700mg BID +

RTV 100mg BID for 14 days and to compare plasma LPV PK following administration of GW433908 1400mg BID + LPV 533mg/RTV 133mg 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 1400mg BID + LPV 533mg/RTV 133mg BID to 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	28 Day Washout	Period 2
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 1400mg BID + LPV 533mg/RTV 133mg 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-three of these 36 subjects completed the study (13 in Arms A and B and 10 in Arms C and D). The overall demographic characteristics of these were as following: Male (64%) and female (36%); White (94%), Black (6%).

INVESTIGATOR AND STUDY LOCATION: [redacted]

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

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

Plasma APV PK Parameter	Treatment 1 Arms A & B (N=13)	Treatment 3 Arms A & B (N=13)
$AUC_{\tau,ss}$ (µg.h/mL)	36.5 (32.0-41.7)	27.2 (21.6-34.2)
$C_{max,ss}$ (µg/mL)	5.72 (5.13-6.39)	4.99 (3.94-6.33)
$C_{\tau,ss}$ (µg/mL)	2.35 (2.02-2.74)	1.35 (1.01-1.81)
$t_{max,ss}$ (h)[a]	2.00 (1.00-5.00)	2.50 (1.00-5.02)

a $t_{max,ss}$ data presented as median (range)
Treatment 1 = GW433908 700mg BID + RTV 100mg BID for 14 days
Treatment 3 = GW433908 1400mg BID + LPV 533mg/RTV 133mg BID for 14 days

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

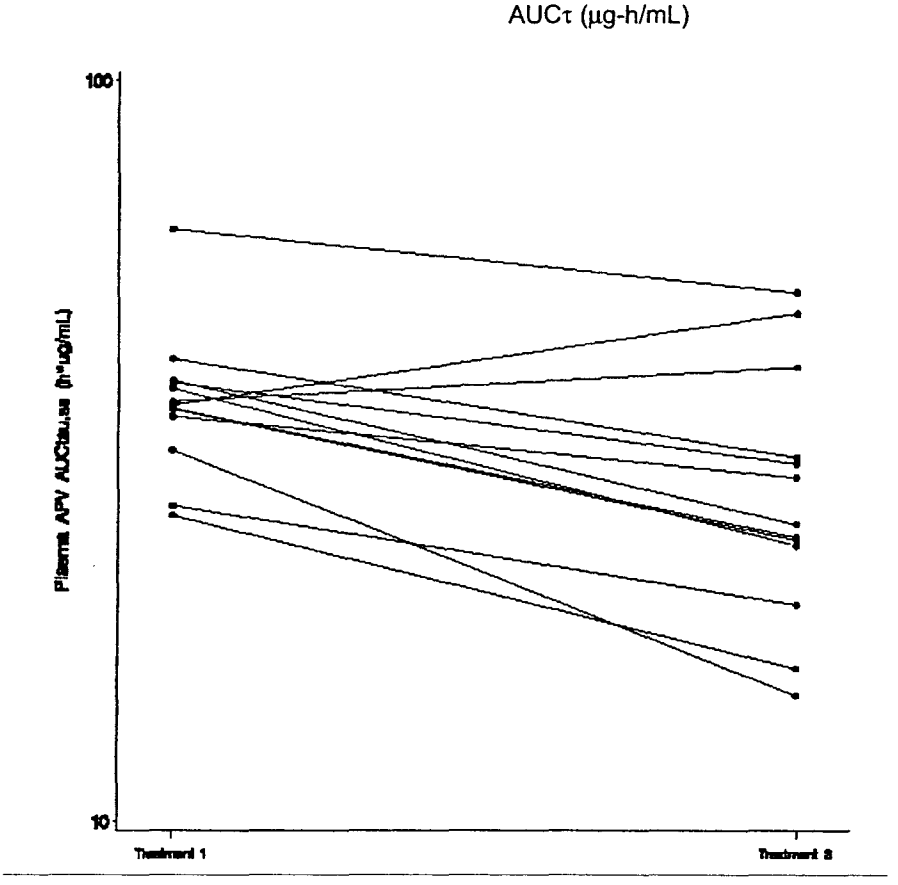
Plasma APV PK Parameter	Treatment 3/Treatment 1 Arms A & B (N=13)
$AUC_{\tau,ss}$ (µg.h/mL)	0.74 (0.65-0.85)
$C_{max,ss}$ (µg/mL)	0.87 (0.74-1.02)
$C_{\tau,ss}$ (µg/mL)	0.58 (0.48-0.70)
$t_{max,ss}$ (h)[a]	1.18 (0.89-1.48)

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

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

Treatment 3 = GW433908 1400mg BID + LPV 533mg/RTV 133mg BID for 14 days

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



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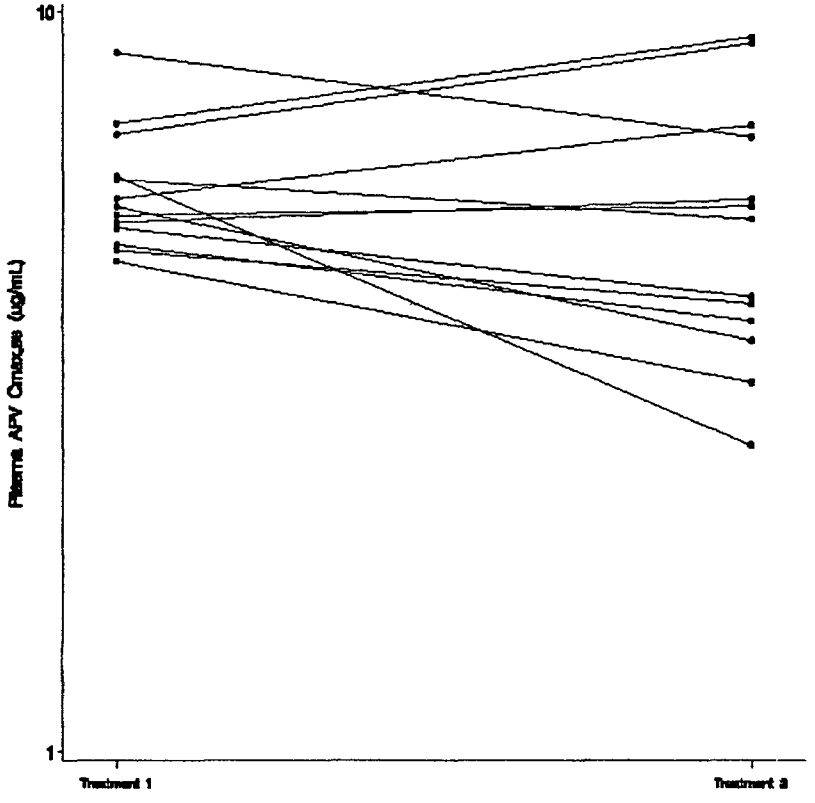

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Cτ (µg/mL)

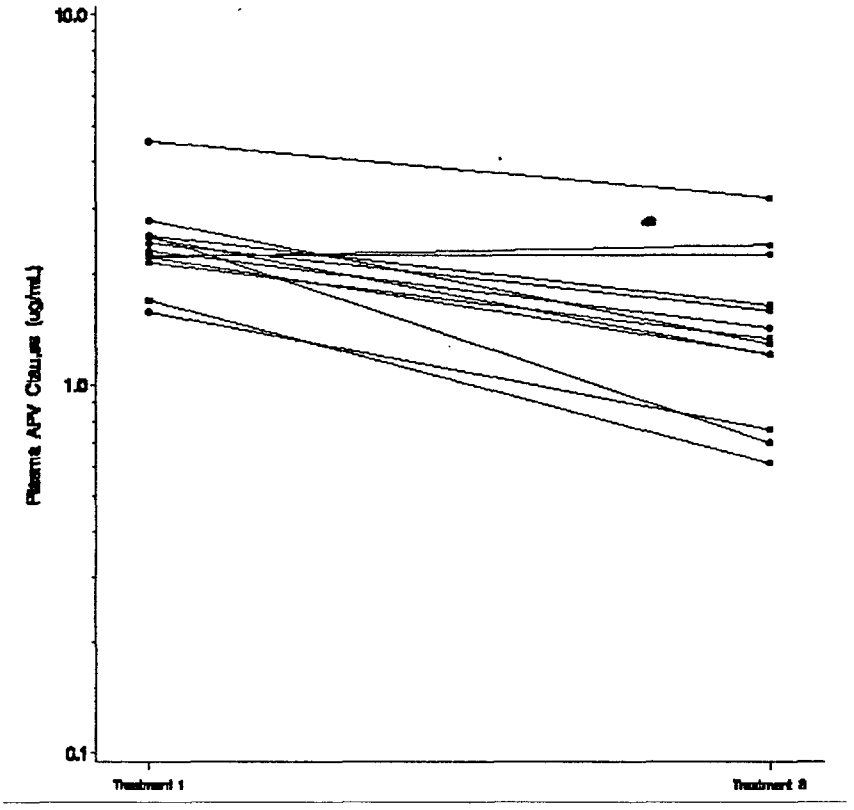

Table 3. Steady-State Plasma LPV PK Parameter Estimates, Geometric Mean (95% CI)

Plasma LPV PK Parameter	Treatment 2 Arms C & D (N=10)	Treatment 3 Arms C & D (N=10)
$AUC_{\tau,ss}$ (µg.h/mL)	92.6 (78.8-109)	83.9 (60.6-116)
$C_{max,ss}$ (µg/mL)	11.3 (9.32-13.6)	10.3 (7.43-14.4)
$C_{\tau,ss}$ (µg/mL)	6.05 (5.13-7.14)	6.07 (4.29-8.61)
$t_{max,ss}$ (h)[a]	4.02 (2.00-5.03)	4.00 (0.00-12.0)

a $t_{max,ss}$ data presented as median (range)
Treatment 2 = LPV 400mg/RTV 100mg BID for 14 days
Treatment 3 = GW433908 1400mg BID + LPV 533mg/RTV 133mg 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)	0.95 (0.67-1.33)
$C_{max,ss}$ (µg/mL)	0.95 (0.66-1.35)
$C_{\tau,ss}$ (µg/mL)	1.01 (0.74-1.39)
$t_{max,ss}$ (h)[a]	1.01 (0.43-1.58)

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

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

Treatment 3 = GW433908 1400mg BID + LPV 533mg/RTV 133mg BID for 14 days

SAFETY RESULTS: GW433908/LPV/RTV combinations studied in APV10011 were poorly tolerated, with a high incidence and increased severity of adverse events. Ten of 36 (28%) subjects enrolled in APV10011 prematurely withdrew from the study due to adverse events; 9 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 DISCUSSION: Coadminstration of LPV 533mg/RTV 133mg BID with GW433908 1400mg BID decreased plasma APV AUC by 26% Cmax by 13%, and Cτ by 42% compared to the GW433908 700mg BID + RTV 100mg BID regimen. Coadminstration of LPV 533mg/RTV 133mg BID with GW433908 1400mg BID provided similar plasma LPV exposure as the LPV 400mg/RTV 100mg BID regimen.

The sponsor also provided the PK summary results of drug-drug interaction studies of Agenerase /Kaletra and Agenerase/ritonavir. These historical PK data indicated that plasma APV concentrations were much lower for Agenerase/LPV/RTV compared to Agenerase/RTV. The interaction between Agenerase and Kaletra seems similar to that of fosamprenavir and kaletra. However, the mechanism by which LPV/RTV decreased plasma APV exposure is unknown. The sponsor conducted several preclinical studies to understand the mechanism. There does not appear to be a physicochemical interaction between the twc products based on similar fosamprenavir release rates during dissolution testing of fosamprenavir in the presence and absence of LPV/RTV. The dissolution profiles for fosamprenavir tablets were comparable in the presence and absence of Kaletra with full release demonstrated within [redacted] Neither LPV nor RTV inhibited human intestinal alkaline phosphatase. Thus, alteration of the conversion of fosamprenavir to APV is not a likely mechanism for the decreased plasma APV exposure observed when fosamprenavir is coadministered with LPV/RTV. Based on the knowledge that all three drugs are inhibiters and inducers of CYP3A4 and are substrates for P-gp and that APV and RTV are also P-gp inducers and inhibitors, the sponsor speculates that the mechanism of the interaction between fosamprenavir and LPV/RTV likely involves a complex balance between the induction and inhibition of metabolic and, potentially, transport processes.

COMMENT TO THE SPONSOR: The mechanisms by which LPV/RTV markedly decreased plasma APV exposure need to be elucidated. We will recommend the sponsor to continue to evaluate the drug-drug interactions between Kaletra and fosamprenavir/ritonavir and to elucidate the underlying mechanisms.