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*APPLICATION NUMBER:*  
**21-548**

**MEDICAL REVIEW**

# **Clinical Review Cover Sheet**

**NDA 21-548**

**Lexiva™ (fosamprenavir calcium) Tablets**

**For: Treatment of HIV infection in adults**

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### I. Recommendations

#### A. Recommendation on Approvability

Based on review of the materials submitted in this NDA, from a clinical perspective this application to market Lexiva™ (fosamprenavir, GW908) for the treatment of HIV-1 infected adults is recommended for approval. This recommendation is based on a thorough review of a robust safety and efficacy database derived from multiple large clinical trials conducted in treatment naïve and PI-experienced HIV-1 infected adults.

#### Benefits

The efficacy data demonstrate that the antiretroviral drug regimen of Lexiva™ (administered with and without ritonavir) plus abacavir and lamivudine in treatment naïve patients was active and produced reductions in viral load as measured by suppression of HIV-1 RNA below detectable levels comparable to other protease inhibitor (PI)-based triple drug regimens. The data also demonstrate that administration of Lexiva twice daily without ritonavir and once daily with ritonavir yielded comparable antiviral efficacy. Specifically, the proportions of patients with HIV-1 RNA <400 c/mL and <50 c/mL in patients who received GW908 without ritonavir were 66% and 57%, and in those who received GW908 once daily with ritonavir, the rates were only slightly higher at 69% and 58%. This clinical benefit was sustained through at least 48 weeks and was generally comparable to a regimen containing Viracept® (nelfinavir, NFV, Agouron Pharmaceuticals), which is generally used as a first-line protease inhibitor. Thus, for treatment naïve patients, GW908 can be administered twice daily without ritonavir, and when a once daily regimen is being considered, GW908/ritonavir once daily provides an option expected to produce similar antiviral activity.

In PI-experienced patients, GW908/ritonavir administered twice daily produced lower reductions from baseline in HIV-1 RNA (the applicant's primary endpoint), -1.39 versus -1.66 log<sub>10</sub> c/mL, but numerically similar proportions of patients with HIV-1 RNA <400 c/mL (58% versus 61%) and <50 c/mL (46% versus 50%) compared to Kaletra® (lopinavir/ritonavir, LPV/r, Abbott Laboratories). Although the study was not large enough to reach a conclusion that GW908/ritonavir twice daily is a clinically equivalent substitute for Kaletra, it provides sufficient information to conclude that Lexiva/ritonavir twice daily is active in this population and is an option available for clinicians and patients to consider.

#### Risks

Fosamprenavir is a prodrug of amprenavir whose adverse event profile is well established. The most common adverse events associated with amprenavir include diarrhea, nausea, vomiting, abdominal pain, headache, fatigue, rash, pruritis, oral and peripheral paresthesia, depression, hepatic transaminitis, and increased cholesterol, triglycerides, and glucose levels. When co-administered with ritonavir, diarrhea, vomiting, fat redistribution, glucose, cholesterol and triglyceride levels are increased in both frequency and severity.

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In treatment naïve patients, use of ritonavir enhanced GW908 has similar efficacy, no advantage in pill count, and an increased frequency of adverse events compared to GW908 alone. However, these limitations should not preclude approval of this regimen. Specifically, it is possible that over a longer duration of exposure the higher levels of GW908 may translate into more durable antiviral responses and delayed emergence of resistance. This hypothesis is based on a finding that no amprenavir resistance-associated mutations emerged in naïve patients who received GW908/ritonavir. Also, once daily administration may be convenient for some patients. Further, although there were increases in triglyceride levels, only two cases of pancreatitis were reported in patients receiving GW908/ritonavir, however, neither patient had elevated triglycerides. In addition, the frequency of rash was somewhat lower among patients who received GW908/ritonavir compared to GW908 alone. Finally, ritonavir enhancement of protease inhibitors is an accepted strategy by clinicians and patients and the increased risks are considered expected and manageable.

In PI-experienced patients, once daily administration of Lexiva/ritonavir led to significantly inferior efficacy compared to Kaletra and GW908/ritonavir twice daily, and is not recommended for use in that population.

In summary, the antiviral and immunologic benefits in both treatment naïve and experienced patients outweigh the risks of generally well characterized and manageable adverse events associated with GW908 and GW908/ritonavir. Thus, GW908 represents an additional option for patients who might benefit from a protease inhibitor-based antiretroviral regimen.

#### **B. Recommendation on Phase 4 Studies and/or Risk Management Steps**

There are no clinical Phase 4 studies. GW908 will be distributed with a patient package insert (PPI).

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## II. Summary of Clinical Findings

Agenerase® is the trade name of the currently approved amprenavir formulations of which there are two: capsules and oral solution. Agenerase is a protease inhibitor with demonstrated efficacy and safety when given in combination with other antiretroviral agents. Agenerase has certain positive attributes, including once and twice daily dosing (i.e., with and without ritonavir boosting), minimal effect of food on amprenavir pharmacokinetics, and a favorable resistance profile. However, low aqueous solubility requiring a formulation that contains a high concentration of vitamin E, a high pill burden (16 capsules daily in adults), and significant gastrointestinal toxicities, have limited its utility in clinical practice.

To reduce the pill burden of Agenerase® (8 capsules BID, 16 total), GlaxoSmithKline developed GW908 (fosamprenavir), a phosphate ester prodrug of amprenavir, which is more water soluble, can be formulated as a film-coated tablet, and can deliver equimolar doses of amprenavir in a substantially reduced pill count (a total of 2 tablets per day).

Ritonavir (Norvir®, Abbott Laboratories) is one of the most potent inhibitors of CYP450 enzyme system and is increasingly being used to pharmacokinetically enhance concomitantly administered protease inhibitors. When co-administered with ritonavir, the dosing of Agenerase is either 600mg (4 capsules)+ritonavir 100mg BID or Agenerase 1200mg (8 capsules)+ritonavir 200mg QD, which provides a moderate decrease in pill counts. Previously reviewed data demonstrated that addition of low doses of ritonavir to Agenerase produced exposures that were similar to exposures produced by the approved dose, 1200mg BID, without significant changes to the types or frequencies of amprenavir-related adverse events.

### A. Brief Overview of Clinical Program

Fosamprenavir is a phosphate ester prodrug of amprenavir, a HIV protease inhibitor, which was developed as an improved formulation for delivery of amprenavir.

The GW908 development program consisted of numerous human clinical pharmacology and three large, randomized clinical trials. In HIV-infected patients naïve to previous antiretroviral therapy studies, GW908 was administered either one daily with ritonavir (APV30002) or twice daily without ritonavir (APV30001). In both studies, all patients received the nucleoside analogues abacavir and lamivudine. In study APV30003, GW908 administered once or twice daily with ritonavir and two nucleoside reverse transcriptase inhibitors (NRTIs) analogues was compared to Kaletra® (lopinavir/ritonavir, LPV/r, Abbott Laboratories) and two NRTIs in patients who had failed at least one previous protease inhibitor (PI) containing regimen.

### B. Efficacy

#### Treatment naïve patients

The results of studies APV30001 and APV30002 demonstrate that GW908 administered twice daily (1400 mg BID), or once daily with ritonavir (1400 mg/ritonavir 200mg QD), in

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combination with abacavir and lamivudine, produced antiviral efficacy consistent with what has been observed with other first line protease inhibitor plus two nucleoside analogue regimens. The GW908 arms in these two studies yielded similar proportion with HIV-1 RNA <400 c/mL (66% and 69%) compared to 52% and 68% in the comparator NFV arms.

Additionally, co-administration of ritonavir appeared to delay the emergence of resistance to GW908. Specifically, in the study in which GW908 was administered alone, five on-therapy HIV-1 isolates from 29 patients with virologic failure showed amprenavir-resistance-associated mutations compared to none of 32 among patients treated with GW908/ritonavir. There are no data, however, on subsequent treatment response among patients who experienced virologic failure while receiving either GW908-based regimen.

#### Treatment experienced patients

In a population of less advanced patients who had previously received antiretroviral therapy with at least one PI-containing regimen, GW908 administered twice daily with ritonavir (700 mg/ritonavir 100 mg BID) with two NRTIs produced an inferior reduction from baseline in HIV-1 RNA, the applicant's primary endpoint, compared to regimens containing Kaletra® and two NRTIs through 48 weeks of therapy (-1.40, versus -1.67 log<sub>10</sub> c/mL). With respect to the secondary endpoints of proportion of patients with HIV-1 RNA <400 and mean increases in CD4 cell counts, GW908/ritonavir produced numerically similar results, 58% and 61% and +47, and +64 cells/mm<sup>3</sup>, respectively. GW908/ritonavir was active and the data support approval of GW908/ritonavir twice daily. However, this study was too small to reach a definitive conclusion that GW908/ritonavir twice daily is a therapeutically equivalent substitute for Kaletra (see Dr. Thomas Hammerstrom's Statistical Review).

Lexiva/ritonavir 1400 mg/200 mg administered once daily was significantly less effective than either twice daily GW908/ritonavir or LPV/r, and is not recommended for treatment experienced patients.

#### **C. Safety**

The most common adverse events reported by patients treated with GW908 (with and without ritonavir) included diarrhea, nausea, vomiting, abdominal pain, headache, fatigue, rash, pruritis, oral and peripheral paresthesia, and depression. Common laboratory abnormalities included hepatic transaminitis, and increased cholesterol, triglycerides, and glucose levels. All of these events were predictable and expected based on preclinical data and data from clinical trials with amprenavir. Co-administration of ritonavir led to increased incidence and severity of diarrhea, vomiting, fat redistribution, and increased glucose, cholesterol and triglyceride levels.

HIV-infected patients are at risk for hepatotoxicity from the disease, antiretroviral therapy, and co-infection with a hepatitis virus. Approximately 6% of patients treated with GW908 experienced Grade 3-4 transaminitis (elevated AST, ALT, or both), with co-infected patients accounting for the majority of events. All patients, but especially those co-infected with hepatitis B and/or C, should be monitored closely during treatment.

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Metabolic abnormalities, including elevated triglycerides, cholesterol, and glucose levels, insulin problems, fat redistribution syndrome (central fat gain and/or peripheral fat loss, buffalo hump and changes in waist/hip ratios), are common in patients receiving PI-based therapy. All were reported among patients receiving GW908; the frequency increased with co-administration of ritonavir. The frequency and severity were within expected parameters, but in treatment experienced patients they were higher than in the comparator arm.

The chemical structure of amprenavir contains a sulfonamide-like moiety. Rash has been reported in amprenavir recipients with sulfonamide allergies in Phase 3 studies. A total of 60/700 (8.5%) of GW908 recipients were known to have a sulfonamide allergy, and rash occurred in 11/60. The median onset and duration were 11 and 13 days, respectively. The majority of patients continued on therapy with subsequent resolution of their rash. One patient with a pre-existing sulfonamide allergy experienced Stevens-Johnson Syndrome; however he was also receiving abacavir and his clinical picture may have been confounded by abacavir hypersensitivity.

#### **D. Resistance**

GW908 has minimal antiviral activity in vitro, and requires metabolic conversion to amprenavir to produce its antiviral activity. Thus in vitro testing for resistance used amprenavir rather than GW908. Genotypic analysis demonstrates that GW908 resistant isolates selected in vitro had one or more mutations in the protease gene resulting in amino acid substitutions at positions M46L, I47V, I50V, and I84V. The I50V substitution alone produces low-level (2-3 fold) resistance to amprenavir. Recombinant viruses which contain triple mutations (M46I + I47V+I50V) exhibited a 15-fold decrease in susceptibility to amprenavir. Co-administration of ritonavir in naive patients (APV30002) appeared to protect against the emergence of resistance compared to the study in which ritonavir was not used (APV30001).

In treatment experienced patients, certain pre-existing PI resistance associated mutations, including M46L, V82A/F/T/S, I54V, and I84V alone or in combination were associated with decreased antiviral response in patients treated with GW908/ritonavir. Further, baseline phenotype data demonstrated that baseline isolates from PI-experienced patients who responded to GW908/ritonavir twice daily had a median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of 0.7 (range: 0.1 to 5.4, n=62), and isolates from individuals failing therapy had a median shift in susceptibility of 1.9 (range: 0.2 to 14, n=29) (see Dr. Lalji Mishra's Microbiology Review).

#### **E. Dosing**

Based on the pharmacokinetic, pharmacodynamic, and clinical data submitted in the NDA, GW908 may be dosed as either 1400 mg twice daily, 1400 mg plus 200 mg of ritonavir once daily, or 700 mg plus 100 mg of ritonavir twice daily to treatment naïve patients. In PI-experienced patients, the recommended dose of GW908 is 700 mg plus ritonavir 100 mg administered twice daily. GW908 may be administered without regard to food.

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The rationale for combining GW908 with ritonavir is to exploit a pharmacokinetic interaction to enable further reductions in the pill burden associated with administration of standard doses of GW908; from two capsules twice daily to either one capsule twice daily or two capsules once daily. Once GW908 is converted to amprenavir in the gut, amprenavir is metabolized in the liver by the CYP3A4 enzyme system. Ritonavir is one of the most potent inhibitors of CYP450 enzyme system and is increasingly being used to pharmacokinetically enhance concomitantly administered protease inhibitors. Ritonavir has been shown to improve the oral bioavailability of protease inhibitors by inhibiting drug-transporting proteins such as P-glycoprotein and decreasing the rate of elimination by inhibition of CYP450 in the liver. In healthy subjects, GW908 700 mg plus ritonavir 100 mg twice daily produces slightly higher amprenavir exposures than GW908 1400 mg plus ritonavir 200 mg once daily; plasma amprenavir exposures were similar in HIV-infected patients.

The GW908 Phase 3 studies were initiated with Tablet Variant A. After initiating these studies, \_\_\_\_\_ was introduced resulting in Tablet Variants B and C, respectively, which were then supplied to the Phase 3 study sites. Tablet Variant C was the proposed the commercial formulation. A subsequent study demonstrated that Tablet Variant B was not bioequivalent to Variant A, and that Variant C was not bioequivalent to Variant B. Thus, Tablet Variant C was not bioequivalent to Tablet Variant A. Despite significant efforts, the applicant has not, to date, been able to explain these results.

Because of the lack of bioequivalence between Tablet Variants A and C, only Tablet Variant A will be approved in this application.

#### **F. Special Populations**

##### **Renal Impairment**

Amprenavir is extensively metabolized with <1% excreted in the urine. Therefore, no dosage adjustment of GW908 is necessary in patients with renal impairment.

##### **Hepatic Impairment**

GW908 has not been studied in patients with hepatic impairment. Because GW908 is rapidly and almost completely converted to amprenavir, dosage recommendations for GW908 in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 8) are based on the results of a previously conducted with amprenavir. Based on these data, the suggested dose of GW908 is 700mg twice daily.

There are no data on use of amprenavir with ritonavir, as either GW908 or Agenerase, in patients with any degree of hepatic impairment, and there are no data on use of GW908 alone in hepatically impaired treatment experienced patients. Therefore, until further data become available, no recommendation for use of GW908 in treatment experienced patients with hepatic impairment can be made. In addition, there are no data on patients with more severe hepatic

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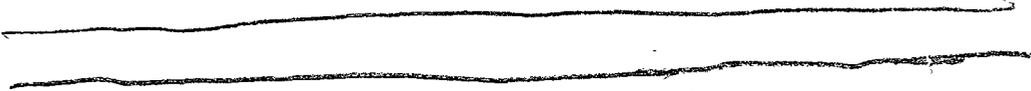
disease (Child-Pugh score 9 to 15), and because of the single strength of GW908 Capsules, no dosing recommendations for these patients can be made.

#### Age

- **Use in Elderly**

There were limited numbers of patients  $\geq 65$  years of age, so it was not possible to assess safety or efficacy in this patient group. Although the numbers of elderly patients with HIV-1 infection was relatively small, there do not appear, from preclinical or clinical studies, any specific contraindications to using GW908 in this age group. Also, elderly patients often have reduced renal function, but GW908 is extensively metabolized with minimum excretion into the urine. Thus no dosing modifications based on older age or renal function is recommended in the labeling.

- **Pediatric Use**



#### Use in Pregnancy

Preclinical testing demonstrated, in rats and rabbits, no major effects on embryo-fetal development, but there was increased incidence of abortion in rabbits. Further, rat pup survival and body weights were reduced. Therefore, GW908 is classified Category C as there are no adequate and well-controlled studies in pregnant women, and it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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### I. Introduction and Background

#### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established name: fosamprenavir calcium  
Trade Name: LEXIVA™  
Chemical: (3S)-tetrahydrofuran-3-yl (1S,2R)-3-[[[4-aminophenyl]sulphonyl](isobutyl)amino]-1-benzyl-2-(phosphonoxy) propylcarbamate monocalcium salt  
Class: Protease Inhibitor  
Proposed Indication: GW908® is indicated in combination with other antiretroviral agents for the treatment of HIV infection  
Age Groups: Adults  
Dose and regimen: 1400 mg twice daily (treatment naïve)  
700 mg with ritonavir 100 mg twice daily (naïve and experienced)  
1400 mg with ritonavir 200 mg once daily (treatment naïve)

#### B. State of Armamentarium for Indication

There are currently 20 drugs approved in the US for the treatment of HIV infection.

The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of compounds to exhibit anti-HIV efficacy. Currently there are 8 NRTI's marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), emtricitabine (Emtriva®), and tenofovir (Viread®), sometimes also referred to as a nucleotide). Additional classes of antiretroviral agents include the non-nucleoside reverse transcriptase inhibitors (NNRTI), including delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®), and the protease inhibitors (PI), represented by indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®), atazanavir (Reyataz®), and lopinavir/ritonavir fixed dose combination (Kaletra®). The first drug in a new class of GP41 fusion inhibitors, enfuvirtide (Fuzeon®), was approved in early 2003.

The current standard is to treat with highly active antiretroviral therapy (HAART) that includes at least three drugs, including either a NNRTI or PI with two NRTIs, to attack various stages in the life-cycle of the virus to attempt long-term suppression of viral replication and increases in CD4 cell counts.

Although the introduction of HAART has led to significant improvement in morbidity and mortality, a substantial number of patients do not achieve or maintain adequate suppression of HIV viral replication. Side effects, drug interactions, and adherence issues such as dosing, pill burden, and complex dietary requirements have been cited as dilemmas facing patients and clinicians.

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Ritonavir improves the oral bioavailability of protease inhibitors by inhibiting drug-transporting proteins such as P-glycoprotein and decreasing the rate of elimination by inhibition of CYP450 in the liver. The use of ritonavir to increase plasma concentrations of protease inhibitors by inhibition of their metabolism by CYP3A4 has been used in order to minimize the development of resistance, overcome the metabolic induction effects of drugs that may be used concomitantly, and possibly improve adherence by having a lower number of tablets required per dose and an option for once daily dosing. The primary clinical chemistry effects of adding low-dose RTV to protease inhibitors include moderate cholesterol, triglyceride and liver transaminase elevations.

There has been interest in the possibility that simplification of regimens might improve tolerability and adherence and increase the feasibility of long-term effective control of disease. Although there are no compliance data available, GW908 could have utility as an additional option for clinicians to consider when designing more simplified HAART regimens.

#### **C. Important Milestones in Product Development**

The fosamprenavir IND (#58,627) was submitted on July 16, 1999.

On September 22, 1999, a clinical development meeting was held. During this meeting it was determined that the use of a single study comparing relative exposure of Agenerase® to fosamprenavir would be not be adequate to register fosamprenavir, and that a clinical study would be required to demonstrate efficacy of fosamprenavir.

The IND was granted Fast Track status on December 1, 1999.

An End of Phase II meeting was held on August 3, 2000. Issues discussed included the applicant's plans for an expanded clinical program consisting of three pivotal clinical studies, two in naive patients and the third in PI-experienced patients. The applicant agreed to incorporate recommendations from DAVDP regarding study endpoints (durable clinical data [24 week with 48 week data to follow], differences in the pharmacokinetic profiles of Agenerase and fosamprenavir, particularly C<sub>max</sub>), consider blinding study arms, use of a 10-12% difference for calculating sample size, definition of the population to be studied (i.e., first-failure, multiple-class failure; etc.), and use of resistance data to guide study design. Overall agreement was reached on proceeding to Phase III. The proposed drug interaction strategy to extrapolate Agenerase data would be acceptable if fosamprenavir/ritonavir interaction data were similar to Agenerase/ritonavir data; if not, additional drug interaction studies would be necessary. The applicant was advised that an appropriate formulation and multiple-dose pharmacokinetic and clinical safety data will be of interest in pediatric patients.

A Pre-NDA meeting was held on October 2, 2002 during which issues for the NDA with respect to tablet bioequivalence and manufacturing controls were discussed. The following agreements were reached: [1] the applicant would conduct a bioequivalence study comparing Tablet Variant A commercial tablet to the Tablet Variant A tablet used in the pivotal clinical studies, [2] additional controls were required to demonstrate a reproducible manufacturing process, [3] results of a pharmacokinetic comparison of Agenerase/ritonavir and fosamprenavir/ritonavir

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would be submitted during NDA review, and [4] the provision of new biopharmaceutics and CMC data could be viewed as major amendments to the NDA and could result in the extension of the review clock.

Discussion of additional key review issues for the NDA occurred on December 20, 2002. Specific items discussed included the need for amendments to the NDA to be submitted by April 30, 2003 (CMC) and May 23, 2003 (biopharmaceutics), the final commercial process to be submitted as a post-approval submission, and that the applicant would provide the production capacity for Table Variant A to support the marketplace (e.g., number of patients that can be supported).

The fosamprenavir NDA (#21-548) was submitted on December 19, 2002, filed on February 3, 2003, and granted a standard (10-month) review period.

The Division of Medication Errors and Technical Support (DMETS) was asked to review the acceptability of the proposed trade name — . DMETS recommended against use of this name because of potential confusion between — and Stelazine. The applicant was advised of this opinion on May 22 and again on September 9, 2003. DAVDP had recommended that the applicant submit alternative names, but it was not until September 12, 2003, that the applicant provided two alternative names: ~~\_\_\_\_\_~~ and Lexiva™; Lexiva™ was subsequently determined to be an acceptable trade name.

#### D. Other Relevant Information

There have been no regulatory approvals for fosamprenavir in markets outside the United States.

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#### E. Important Issues with Pharmacologically Related Agents

GW908 (fosamprenavir) is a prodrug of amprenavir. Amprenavir is currently approved in the US as Agenerase® Capsules and Oral Solution. The Agenerase NDA was approved in the US in April 1999, and both formulations are approved for use in patients three years of age and older in Switzerland, Israel, Japan, Brazil, Mexico, Uruguay, Chile, Argentina, Columbia, Ghana, Madagascar, Malawi, and the European Union. In January 2002, recommendations for dosing Agenerase Capsules with ritonavir were added to the labeling.

The FDA Adverse Event Reporting System was searched during the review of the GW908 NDA to look for new or different adverse events among patients receiving Agenerase with and without ritonavir. The events reported were consistent with the known amprenavir adverse event profile, and no new events were identified.

Lipodystrophy, hypertriglyceridemia, hypercholesterolemia, hyperglycemia, diabetes mellitus, hemolytic anemia, increased bleeding in hemophiliacs have been identified as related to treatment with protease inhibitors, and have been reported in patients treated with amprenavir.

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#### II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Fosamprenavir is the phosphate ester prodrug of amprenavir. Amprenavir is a selective inhibitor of the HIV-1 aspartyl protease, and is classified as a protease inhibitor (PI). Fosamprenavir calcium is a single stereoisomer with the (3S)(1S,2R) configuration. It has a molecular formula of C<sub>25</sub>H<sub>34</sub>CaN<sub>3</sub>O<sub>9</sub>PS and a molecular weight of 623.7. GW433908 is a calcium salt of amprenavir that is hydrolyzed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium.

#### Animal Pharmacology and Toxicology

For an in-depth discussion, please see Dr. Hao Zhang's pharmacology/toxicology review. For the purpose of the pharmacology/toxicology review, data on the parent compound, GW908 is presented. Important pharmacological/toxicological findings include:

- Following a single oral dose, the NOAEL of fosamprenavir in mice was  $\geq 2000$  mg/kg (equivalent to a human dose of  $\geq 180$  mg/kg/day based on body surface area). Reversible toxicities included microscopic liver changes, consistent with the toxicology profile of amprenavir.
- Multiple dose toxicity observed in 14-day and 4-week dog studies included salivation, vomiting, soft to liquid feces, dehydration and electrolyte imbalances. Further, there was evidence of electrocardiographic changes (ventricular bigeminy, increased QT interval, increased U waves, and T-wave notching) thought to be secondary to electrolyte (potassium) imbalances due to gastrointestinal toxicity. No electrocardiographic changes were observed in a 9-month dog study or in humans.
- Serum clinical chemistry changes in rats and dogs attributable to fosamprenavir included increased cholesterol, decreased triglycerides, and increased serum AST, ALT, GD and GGT levels.
- Fosamprenavir is not a mutagen and is not genotoxic.
- Pregnancy Category C. Administration of fosamprenavir to pregnant rats and rabbits produced no major effects on embryo-fetal development; however, the incidence of abortion was increased in pregnant rabbits. Fosamprenavir caused a reduction in both rat pup survival and body weights. Further, surviving F<sub>1</sub> female rats showed an increased time to successful mating, an increased length of gestation, a reduced number of uterine implantation sites per litter, and reduced gestational body weights compared to control animals.

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### Chemistry, Manufacturing and Controls

For an in depth discussion, please see Dr. George Lunn's review.

Fosamprenavir is the calcium salt of the phosphate ester prodrug of amprenavir. The sodium salt was used in very early studies but the calcium salt was soon found to have superior properties. All tablets have had the same basic composition with only minor changes in the excipient ratios. The manufacturing process has remained essentially unchanged throughout development. Manufacturing involves \_\_\_\_\_

The drug product is a pink, film-coated 700 mg tablet that is capsule shaped (approx 20.5 x 9.5 mm), with GX LL7 debossed on one face. The composition of each tablet is listed in Table 1.

**Table 1. Composition of Lexiva™ Tablets**

Component	Weight (mg)/ Tablet
GW433908G	—
Microcrystalline cellulose, NF	—
Croscarmellose, NF	—
Providone K30, USP	—
Magnesium stearate, NF	—
Colloidal Silicon Dioxide, NF	—
_____	—
_____	—
<b>Total Target Weight</b>	—

<sup>a</sup> The weight of the calcium salt ( — ) is equivalent to 700 mg of the parent phosphoric acid and 600 mg amprenavir.

The process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the pivotal clinical studies. However, the most important CMC/clinical issue is the lack of bioequivalence between tablets made from drug substance manufactured on a \_\_\_\_\_ scale ( — Tablet Variant A) and on a \_\_\_\_\_ scale ( — Tablet Variants B and C). This difference remains unexplained. The applicant has opted to proceed with Tablet Variant A manufactured from drug substance made on the \_\_\_\_\_ scale. Drug substance made on a \_\_\_\_\_ scale will only be used after this NDA is approved and after the submission (and approval) of a Prior Approval Supplement (see **Human Pharmacokinetics and Pharmacodynamics** below).

The regulatory specification for Lexiva™ Tablets includes description, identification, assay, content uniformity, chromatographic impurity/degradation products, polymorphic form, dissolution, and microbial attributes, which were found to be generally acceptable.

The qualification levels of a number of impurities were less than the proposed limits when the No Observed Adverse Event Levels (NOAEL) found in the non-clinical toxicity studies in rats and dogs were considered. The applicant calculated the drug substance qualification levels based

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on the high dose used in a 14-day rat study, rather than the NOAEL in the non-clinical toxicology studies. However, such a calculation was not acceptable because at such doses toxicity was seen in the animals. The applicant has committed to qualify the impurities at an appropriate level in a 90-day rat toxicity study as a Phase 4 commitment. For further details see Dr. Hao Zhang's Pharmacology/Toxicology review.

Of note, tablets stored in open bottles at 30°C/60% relative humidity and 40°C/75% relative humidity

Since dissolution data were not available it was not possible to know if this affected dissolution. The phrases "keep bottle tightly closed" or "dispense only in original container" will be added to the container label. The  of tablets stored in closed containers does not change significantly.

Despite these findings, the data submitted support a shelf-life of 30 months for Lexiva™ Tablets packaged in HDPE bottles when stored at 25°C (77°F) with excursions permitted to 15°C and 30°C (59-86°F).

Pre-Approval inspections of all manufacturing facilities for the NDA were found acceptable.

### Microbiology

For an in depth discussion, please see Dr. Lalji Mishra's review. Fosamprenavir is rapidly and almost entirely (99%) converted to amprenavir; thus, microbiological data for amprenavir are applicable to fosamprenavir.

- Amprenavir inhibits recombinant HIV-1 protease with a  $K_i$  value of 0.6 nM and does not substantially inhibit cellular aspartic proteinases pepsin, cathepsin D, and renin. Amprenavir binds to the active site of HIV-1 protease and thereby prevents the processing of viral Gag and Gag-Pol polyprotein precursors, resulting in the formation of immature non-infectious viral particles.
- Amprenavir exhibits anti-HIV-1 activity both in vitro and in vivo. The anti-HIV-1 activity of amprenavir varied with cell types, multiplicity of infection and assay conditions used. The  $IC_{50}$  values of amprenavir against HIV-1 IIIB ranged from 0.012 to 0.41  $\mu$ M. The  $IC_{50}$  value of amprenavir against HIV-1 clinical isolates (n=9) ranged from 0.0008 to 0.0380  $\mu$ M.
- In cell culture studies, amprenavir exhibited synergistic anti-HIV-1 activity in combination with zidovudine, didanosine, abacavir, or saquinavir, and additive anti-HIV-1 activity in combination with indinavir, nelfinavir, or ritonavir.
- Genotypic analysis show that amprenavir resistant isolates selected in vitro have one or more mutations in the protease gene resulting in amino acid substitutions at positions M46L, I47V, I50V, and I84V. The I50V substitution alone produces low-level (2-3 fold)

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- resistance to APV. In contrast, recombinant viruses which contained triple mutations (M46I + I47V+I50V) exhibited a 15-fold decrease in susceptibility to amprenavir.
- Patients with the I84V, V82A/F/T/S or I54V mutation present at baseline had lower treatment responses compared to Kaletra®.
  - Baseline phenotype data demonstrated that baseline isolates from PI-experienced patients who responded to GW908/ritonavir twice daily had a median shift in susceptibility to amprenavir relative to a standard wild-type reference strain of 0.7 (range: 0.1 to 5.4, n =62), and isolates from individuals failing therapy had a median shift in susceptibility of 1.9 (range: 0.2 to 14, n =29).

### III. Human Pharmacokinetics and Pharmacodynamics

Please see Dr. Derek Zhang's review for an in-depth discussion of the pharmacokinetics and pharmacodynamics of fosamprenavir.

#### A. Pharmacokinetics

- In humans, fosamprenavir is rapidly and almost entirely (99%) converted to amprenavir at or near the intestinal epithelium via alkaline phosphatase, with minimal plasma fosamprenavir exposure (fosamprenavir AUC <0.6% of corresponding amprenavir AUC).
- Equimolar doses of fosamprenavir (1400mg) and Agenerase (1200mg) deliver comparable plasma amprenavir exposures except with lower  $C_{max}$  values by fosamprenavir 1400mg.
- Single dose plasma amprenavir pharmacokinetics are not predictive of steady-state pharmacokinetics. Similar to observations in prior Agenerase studies, plasma amprenavir AUC values decrease over time following multiple-dose administration of fosamprenavir, with steady state reached in two weeks.
- The absolute bioavailability of amprenavir from fosamprenavir cannot be determined because a conversion step from fosamprenavir to amprenavir is necessary.
- Amprenavir is extensively metabolized by CYP3A4 with minimal unchanged amprenavir excreted in urine. No dosage regimen adjustments are necessary for patients with renal dysfunction.
- Amprenavir is widely distributed in body tissues and is bound to plasma proteins, primarily  $\alpha$ 1-acid glycoprotein (AAG), by approximately 90%.
- Amprenavir is a substrate for P-glycoprotein.

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- Fosamprenavir capsules may be administered without regard to food intake.
- Coadministration of fosamprenavir with ritonavir increases plasma amprenavir exposure (AUC and  $C_{min}$  increased by 50% and 4 to 6-fold on average, respectively) primarily through inhibition of amprenavir metabolism, thus maximizing and maintaining plasma amprenavir concentrations above the  $IC_{50}$  for amprenavir against HIV from patients with various levels of HIV protease inhibitor experience, including PI-naïve and multiple-PI-experienced patients.
- Amprenavir is a CYP3A4 substrate and inhibitor, and potentially a mild CYP3A4 inducer. Thus, caution should be exercised when co-administration of substrates, inducers or inhibitors of CYP3A4 enzyme with fosamprenavir or fosamprenavir/ritonavir.
- Co-administration of fosamprenavir 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 fosamprenavir because they reduce plasma concentrations of amprenavir to suboptimal levels and may lead to loss of virologic response and possible resistance to fosamprenavir.
- Concomitant use of fosamprenavir with lovastatin or simvastatin is not recommended. Caution should be exercised if fosamprenavir 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 fosamprenavir is used in combination with these drugs.
- Caution should be used when prescribing sildenafil or vardenafil in patients receiving fosamprenavir. Co-administration of fosamprenavir with these agents is expected to substantially increase their concentrations and may result in an increase in sildenafil-associated adverse events, including hypotension, visual changes, and priapism.
- Co-administration of efavirenz with fosamprenavir with 200mg of ritonavir decreased plasma amprenavir and ritonavir exposures. The addition of an additional 100mg of ritonavir (300 mg total) resulted in plasma amprenavir concentrations similar to those achieved when fosamprenavir and ritonavir were administered without concomitant efavirenz.
- Fosamprenavir solubility is significantly reduced at pH greater than 5. Co-administration of fosamprenavir with drugs that increase gastrointestinal pH, such as Maalox TC and ranitidine medications (including histamine<sub>2</sub> receptor antagonists and acid neutralizers), resulted in statistically significant reductions in plasma amprenavir exposure. The mechanism of this is likely due to changes in gastric pH and phosphate binding that could affect fosamprenavir

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solubility and subsequent plasma amprenavir pharmacokinetics. Thus antacids and fosamprenavir should not be co-administered.

- Plasma amprenavir and lopinavir exposures markedly decreased when LPV/ritonavir was co-administered with either fosamprenavir or Agenerase. The interactions for fosamprenavir and amprenavir seem similar, however the underlying mechanisms remain unknown.
- Dose reduction is recommended in patients with mild and moderate hepatic impairment because plasma amprenavir 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.
- Plasma amprenavir pharmacokinetics are similar based on demographic factors such as sex, race, age, and body weight, and between healthy and HIV-infected adults.

#### Formulation Issues

The Lexiva™ Phase 3 studies were initiated with Tablet Variant A. After initiating these studies,                      was introduced resulting in Tablet Variants B and C, respectively, which were then supplied to the Phase 3 study sites. Tablet Variant C was the proposed the commercial formulation. Bioequivalence of Tablet Variant B to Variant A and Variant C to Variant B was not achieved. Thus Tablet Variant C was not bioequivalent to Tablet Variant A. Despite significant efforts, the applicant has not, to date, been able to explain these results.

Because of the lack of bioequivalence between Tablet Variants A and B and B and C, the applicant proposed in the NDA to market a 700mg tablet (Tablet Variant A) manufactured in                      batches with drug substance manufactured in                      batches. To support this proposal, the applicant submitted results from study APV10021, which demonstrated that Tablet Variant A used to initiate the pivotal Phase 3 studies is bioequivalent to the proposed to be marketed Tablet Variant A.

#### B. Pharmacodynamics

The selection of the 1395 mg fosamprenavir dose (2 x 700 mg tablets) for use in clinical studies was based on data from study APV20001. In this study, 84 subjects who had received minimal previous NRTI or NNRTI therapy and no prior PI therapy were randomized to one of four arms:

- fosamprenavir 1395mg BID followed by Agnerease 1200mg BID
- Agenerase 1200mg BID followed by fosamprenavir 1395mg BID
- fosamprenavir 1860mg BID followed by Agenerase 1200mg BID
- Agenerase 1200mg BID followed by fosamprenavir 1860mg BID

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One fosamprenavir 465mg tablet contains 400mg amprenavir molar equivalents. The 1395mg dose contains 1200mg amprenavir molar equivalents, and the 1860mg dose contains 1600mg amprenavir molar equivalents.

The dosing period for each drug was 28 days. All patients also received 3TC+abacavir. Following completion of the two dosing periods, patients were allowed to receive open label Agenerase alone or in combination with ritonavir for an additional 42 weeks (48 weeks total).

Both the fosamprenavir 1395mg and 1860mg twice daily doses delivered equivalent plasma amprenavir  $AUC_{\tau,ss}$  values, lower  $C_{max,ss}$  values (~30% lower), and higher  $C_{\tau,ss}$  values (~28% higher for fosamprenavir 1395mg twice daily and ~46% higher for fosamprenavir 1860mg twice daily) as compared to Agenerase 1200mg twice daily.

Median change in HIV-1 RNA from baseline at day 28 was -2.0, -1.9, and -2.0  $\log_{10}$  c/mL for the 1395mg twice daily, 1860mg twice daily and Agenerase twice daily groups, respectively. The median change from baseline in CD4 cell counts was +111 in the 1395mg group, +106 in the 1860mg group, and +92 cells/mm<sup>3</sup> in the Agenerase group. There were no safety differences between dose groups.

To support co-administration with ritonavir, a study in healthy adults was conducted that demonstrated the GW908 700mg BID+ritonavir 100mg twice regimen delivered slightly higher plasma amprenavir  $AUC_{24,ss}$ , slightly lower  $C_{max,ss}$ , and moderately higher  $C_{min,ss}$  values compared to the GW908 1400mg QD+RTV 200mg once daily regimen.

In summary, these data supported the GW908 1400mg twice daily dose since there was no apparent increase in efficacy for the 1860mg twice dose, and the proposed doses of GW908 when co-administered with ritonavir.

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### IV. Description of Clinical Data and Sources

#### A. Overall Data

The data to support the safety and efficacy of Lexiva for treatment of adults with HIV-1 infection were derived from three clinical studies conducted by the applicant. In addition, the applicant included in the NDA brief reports from a number of ongoing clinical studies in which HIV-infected patients are receiving Lexiva™.

#### B. Tables Listing the Clinical Trials

Table 2 presents a schematic overview of the three principal clinical studies submitted to support the safety and efficacy of GW908.

**Table 2. Pivotal Lexiva™ HIV Studies**

Protocol No. Population Countries	Start Date End Date	Design	Treatment Dose Frequency Duration	No. Patients Treated
APV30001  Treatment naïve  US, Puerto Rico, Panama, South Africa	November 2000 August 2002	Randomized, open-label	GW908+ABC+ 3TC  NFV+ABC+3TC  48 weeks	GW908: 166  NFV: 83
APV30002  Treatment naïve  US, Europe, South Africa	November 2000 August 2002	Randomized, open-label	GW908/ritonavir QD+ABC+3TC  NFV+ABC+3TC  48 weeks	GW908: 322  NFV: 327
APV30003  PI failures  U.S., Europe, Australia, Canada, Puerto Rico	May 2001 February 2003	Randomized, open-label	GW908/ritonavir QD+2 NRTI  GW908/ritonavir BID+2 NRTI  LPV/ritonavir BID+2 NRTI  48 weeks	GW908/r QD: 107  GW908/r BID: 105  LPV/r: 103

#### C. Postmarketing Experience

GW908 is not currently approved for marketing in any country.

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#### V. Clinical Review Methods

##### A. How the Review was Conducted

NDA 21-548 for Lexiva™ Tablets was submitted electronically. In addition, responses to requests for additional clinical, virological, and pharmacologic information were reviewed.

The indication proposed by the applicant was treatment of HIV-1 infection in \_\_\_\_\_  
\_\_\_\_\_ However, insufficient numbers of patients \_\_\_\_\_ actually enrolled in clinical trials, so the indication will be revised to state that Lexiva is indicated for use in adults. As noted in Table 2 above, the development program to support the safety and efficacy of GW908 consisted of three pivotal studies. Study reports, line listings, and Case Report Forms were reviewed for all efficacy endpoints and demographic subgroups. The safety review also consisted of a review of all adverse events by summary tables and line listings, along with review of physical examination line listings. 'Clinically significant' laboratory abnormalities were defined as falling outside the 'normal' range values for the parameter by a specified amount defined in the study reports.

An update containing additional safety information (safety cut off February 12, 2003) and the 48-week results of study APV30003 were submitted during the review period (August 11, 2003), as were individual Serious Adverse Event reports from ongoing studies.

Pertinent positive and negative safety and efficacy findings are discussed in the clinical study reviews. Additional human safety information derived from pharmacokinetics studies and from other specific safety-related investigations is discussed in the integrated summary of safety section. The medical reviewer's recommendations for approval are summarized in the **Conclusions and Recommendations** section.

##### B. Overview of Materials Consulted in Review

The primary materials consulted included the entire NDA and IND, protocols and reports of studies conducted by the applicant that included Emtriva, and responses to requests for additional information to the NDA. The NDA and responses to requests for additional information were submitted in both hard copy and to the electronic document room. In addition, a 120 day safety update was submitted on April 18, 2003.

##### C. Overview of Methods Used to Evaluate Data Quality and Integrity

Dr. Steven Kooshian (study APV30001) in Long Beach, California, underwent a "for cause" inspection by the Division of Scientific Investigations (DSI). The applicant notified DSI that Dr. Kooshian's IRB had closed his study site due to inaccurate responses to an IRB questionnaire about sanctions taken against him by the State Medical Board. At the time the site was closed, Dr. Kooshian had enrolled one patient. The DSI inspector found that Dr. Kooshian "did not

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adhere to applicable statutory and FDA requirements governing the conduct of clinical investigations and protection of human subjects." Specifically, Dr. Kooshian failed to collect pharmacokinetic blood samples at protocol-defined times. DSI recommended that the data from Dr. Kooshian's site not be used in the review of this NDA. When all above efficacy endpoints were analyzed with the one patient from Site 10 (Dr. Kooshian) removed, there was no difference in the results.

**Comment: Efficacy analyses including and excluding the one patient from Dr. Kooshian's site yielded similar results. Given the rather serious infractions identified, this patient will be excluded from the efficacy analysis, but will be included in the review of safety.**

#### D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies appeared to have been conducted under Good Clinical Practices conditions.

#### E. Evaluation of Financial Disclosure

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed. The applicant requested that all investigators and sub-investigators from all studies contained in the NDA to disclose proprietary interest or significant equity as defined in the regulations. The applicant has included a list of all investigators and sub-investigators who responded to their request on form 3454.

Based on available financial data, the \$25,000 threshold for payments of other sorts was exceeded by only 1 investigator in the APV30002 study and 2 investigators in study APV30003. Each investigator enrolled <1% of total study patients.

- Dr. \_\_\_\_\_ based at the \_\_\_\_\_ (site id. 4954) enrolled 5/649 subjects in APV30002.
- Dr. \_\_\_\_\_ based in \_\_\_\_\_ (site id. 23977) enrolled 2/315 subjects in APV30003.
- Dr. \_\_\_\_\_ (sub-investigator for \_\_\_\_\_, based at the \_\_\_\_\_ (site id. 45217) enrolled 1/315 subjects in APV30003.

In the APV30002 study the \$50,000 threshold for equity interest was exceeded in the case of one investigator:

- Dr. \_\_\_\_\_ based in \_\_\_\_\_ (site id. 20130) enrolled 4/649 subjects in APV30002, representing <1% of study patients.

**Comment: Each of the above individuals were sub-investigators in large double-blind, placebo-controlled multi-center studies, each enrolled very few patients, and none were**

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involved in the analysis of study data. Therefore, it does not appear that the financial interests of these sub-investigators impacted the results of the studies.

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#### VI. Integrated Review of Efficacy

##### A. Brief Statement of Conclusions

In treatment naïve patients, the two Lexiva™ regimens (1400mg twice daily and 1400mg plus 200mg ritonavir once daily) produced comparable antiviral and immunologic activity as evidenced by similar reductions from baseline in HIV-1 RNA (-2.17 and -2.25 log<sub>10</sub> c/mL), similar proportions of patients with HIV-1 RNA <400 c/mL (66% and 69%), <50 c/mL (57% and 58%), and similar mean increases in CD4 cell counts (+139 and +137 cells/mm<sup>3</sup>).

In patients who had previously received antiretroviral therapy with at least one PI-containing regimen, GW908 administered twice daily with ritonavir (700 mg/ritonavir 100 mg BID) with two NRTIs produced an inferior reduction from baseline in HIV-1 RNA, the applicant's primary endpoint, compared to regimens containing Kaletra® and two NRTIs through 48 weeks of therapy but numerically similar proportions of patients with HIV-1 RNA <400 and mean increases in CD4 cell counts. However, this study was too small to reach a definitive conclusion that GW908/ritonavir twice daily is a clinically equivalent substitute for Kaletra.

Once daily GW908/ritonavir was significantly less effective than either twice daily GW908/ritonavir or LPV/r, and is not recommended for treatment experienced patients.

##### B. General Approach to Review of the Efficacy of the Drug

The principle focus of the review were the three clinical trials in which 700 treatment naïve and experienced patients received GW908 for up to 48 weeks (see Table 2). Supportive controlled and uncontrolled studies were evaluated for any usable efficacy information.

##### C. Detailed Review of Trials by Indication

The applicant has requested an indication for treatment of HIV-1-infected patients, and this is the only indication sought in the application. The three pivotal efficacy studies (APV30001, APV30002 and APV30003) submitted in support of this indication are reviewed in detail below.

**Comment: The applicant did not specify the age of patients for which approval is being sought. The lower age of patients enrolled in these studies was 18. Therefore, the indication will be limited to adults.**

##### C.1 Review of Pivotal Efficacy Studies

##### C.1.a Study APV30001

The study was a phase 3, randomized, multicenter, parallel, open-label study to compare the efficacy, safety and tolerability of GW908® (1400mg twice daily) and Viracept® (1250mg twice daily, [Agouron Pharmaceuticals, nelfinavir, NFV]) over 48 weeks in antiretroviral therapy-naïve HIV-1 infected adults.

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This study was conducted at 29 sites in the United States, Puerto Rico, Panama, and the Republic of South Africa between November 14, 2000 and August 14, 2002.

#### Objectives

The primary objective was to compare the efficacy and durability of the antiviral response of Lexiva and NFV when administered in combination with abacavir (ABC) and lamivudine (3TC).

Secondary objectives were to compare: the safety and tolerability of GW908 and NFV when administered in combination with ABC and 3TC; virologic response; immunologic response; occurrence of events related to metabolic abnormalities between treatment groups; and, to assess the development of viral resistance in a subset of patients following treatment.

#### Design

Study APV30001 was a randomized, open-label study in HIV-1 infected, antiretroviral therapy-naïve patients (defined as having had less than 4 weeks [28 days] therapy with any NRTI and no previous therapy with any NNRTI or HIV PI). Patients participated in a screening period (up to day 28), a randomized treatment period (day 1 until the last subject enrolled completed the Week 48 visit) and a follow-up period (conducted 4 weeks after discontinuation from the study).

Patients were randomized to one of the following treatment groups in a 2:1 manner and stratified by screening plasma HIV RNA (5000-10,000 copies/mL, >10,000-100,000 copies/mL and >100,000 copies/mL):

Group 1: GW908 1400mg BID + ABC 300mg BID + 3TC 150mg BID  
Group 2: NFV 1250mg BID + ABC 300mg BID + 3TC 150mg BID

A patient could change therapy if their plasma HIV RNA remained >1000 copies/mL at week 16, or had previously been undetectable (<400 copies/mL) and subsequently rebounded to >1000 copies/mL after week 16 on a confirmatory sample collected within 4 weeks.

Patients intolerant to their randomized PI and who required permanent discontinuation of the PI were not allowed to switch to another PI, and were discontinued from the study. Patients prematurely discontinued from the study were not replaced. Patients intolerant to ABC or 3TC were allowed to change to other approved NRTIs and continue in the study. Tablet Variants A and B were used in this study.

#### Demographics and Disposition

To be included, patients had to be male or female 13 years of age or older (or 18 years of age or older according to local requirements); naïve to antiretroviral therapy following documented HIV infection (<4 weeks [28 days] therapy with any NRTI and received no prior NNRTI or PI); and a screening plasma HIV-1 RNA  $\geq$ 5000 copies/mL. Female subjects must have been of: a non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including post-

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menopausal status) or of child-bearing potential with a negative pregnancy test at screen and who agreed to use a proven barrier method of contraception (e.g., spermicide plus condom).

The demographic and disease characteristics of study patients are presented in Table 3.

**Table 3 Demographics and disease characteristics, APV30001**

	GW908+ABC+3TC (n=166)	Nelfinavir+ABC+3TC (n=83)
<b>Age</b>		
<b>Median (range)</b>	37 (17, 70)	39 (22, 65)
<b>Gender</b>		
<b>Male</b>	69%	69%
<b>Female</b>	31%	31%
<b>Race</b>		
<b>White</b>	25%	20%
<b>Black</b>	31%	33%
<b>Asian</b>	<1%	0
<b>American Hispanic</b>	43%	46%
<b>Other</b>	0	1%
<b>HIV RNA (log<sub>10</sub> c/mL)</b>		
<b>Median (range)</b>	4.82 (1.69-7.41)	4.85 ( — )
<b>≥1,000-10,000</b>	9%	10%
<b>10,000-100,000</b>	47%	46%
<b>&gt;100,000</b>	44%	44%
<b>CD4 cells/mm<sup>3</sup></b>		
<b>Median (range)</b>	214 (2-1136)	212 ( — )
<b>CDC Classification</b>		
<b>B</b>	18%	16%
<b>C</b>	20%	19%
<b>Hepatitis C reactive</b>	13%	17%
<b>Hepatitis B reactive</b>	5%	5%

Of the patients with baseline HIV-1 RNA >100,000 c/mL, approximately 15% had very high levels, >500,000 c/mL.

There were relatively high proportions of Hispanic and Black patients enrolled, which may have been a function of the locations in which the study was conducted, i.e., Latin and South America and South Africa. However, the results of the study are important for the US since Blacks and Hispanics represent the fastest growing populations of HIV infected persons. Comparison of baseline characteristics by gender showed that most of the male enrollees were Caucasian and most females were Black.

**Comment:** The treatment groups were generally well balanced with regard to demographic and disease characteristics at baseline, and represented a somewhat more advanced population of naive patients than typically enroll in studies conducted solely in the US. This finding may have been a function of the study locations since access to the HIV medical infrastructure may be limited and antiretroviral drugs tend to be less readily available in South Africa and parts of Latin America.

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Table 4 presents the applicants' assessment of patient disposition.

**Table 4. Patient disposition through 48 weeks (applicant's analysis), APV30001**

	GW908+ABC+3TC	Nelfinavir+ABC+3TC
Randomized	168	83
Received at least one dose of study medication	166	83
Completed 48 weeks on randomized PI	116 (70%)	45 (54%)
Discontinued randomized PI	50 (30%)	38 (46%)
-Adverse event	9 (5%)	6 (7%)
-Consent withdrawn	6 (4%)	3 (4%)
-Lost to follow-up	18 (11%)	7 (8%)
-Clinical progression	1 (<1%)	1 (1%)
-Insufficient viral load response	12 (7%)	16 (19%)
-Other	4 (2%)	5 (6%)

Overall the reasons for discontinuation were similar across the arms with the exception of over twice as many patients discontinuing NFV due to insufficient viral load response. There was no specific pattern to the type or timing of adverse events leading to discontinuation from the GW908 arm.

Review of individual patients identified a number of discrepancies between the applicant's assessment of reasons for premature discontinuation and the reasons listed on various outcomes and disposition tables. Two patients in the GW908 arm and three in the NFV arm were experiencing adverse events that could reasonably be attributed to their study regimen at the time they withdrew consent. Diarrhea and waxy feeling in mouth accounted for the changes in the GW908 arm and the changes in the NFV arm were due to headache, diarrhea, and depression. Additionally, two patients in the GW908 arm and one patient in the NFV arm classified as consent withdrawn had study medications permanently discontinued due to HIV-1 plasma RNA rebound. The "Other" reasons for discontinuation from the NFV arm included two patients who relocated and three who had poor compliance with study procedures. In the GW908 arm the "Other" reasons were poor compliance (n=4) and pregnancy (n=1).

### Endpoints, Analyses and Results

For a detailed discussion and analysis of the efficacy results, please see Dr. Thomas Hammerstrom's statistical review.

The primary efficacy endpoint was the proportion of patients with HIV-1 RNA <400 c/mL at week 48. Additional secondary efficacy endpoints included:

- Proportion of subjects with plasma HIV-1 RNA levels <50 c/mL at week 48.
- Measured values, absolute changes from baseline and average area under the curve minus baseline (AAUCMB) in plasma HIV-1 RNA over time.
- Measured values, absolute changes from baseline and average area under the curve minus baseline (AAUCMB) in CD4+ cell counts over time.

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- Progression of HIV disease as measured by CDC Classifications and deaths.
- Genotypic/phenotypic analysis of selected viral isolates.

The study was powered on the secondary endpoint of plasma HIV-1 AAUCMB. Using a non-inferiority margin of 0.5 log<sub>10</sub> c/mL, and assuming a standard deviation in plasma HIV RNA of 0.7 log<sub>10</sub> c/mL, with a planned sample size of 210 patients (140 to GW908 and 70 to NFV) the applicant surmised the results would provide 99% power to test the non-inferiority of GW908 to NFV at a 2.5% significance level.

The applicant used the Amplicor® HIV-1 Ultrasensitive Monitor (Roche Diagnostics) Test (Primers 1.5, ultrasensitive LOD [limit of detection] =50 c/mL). Samples with >75,000 c/mL were retested using the Amplicor® HIV-1 Monitor Test (Primers 1.5, standard assay LOD=400 c/mL).

Table 5 reflects the overall results of the study and contains the data that will be included in the labeling. In Table 5, the category “Discontinued due to Adverse Events” reflects the re-categorization of two GW908 and two NFV patients who withdrew consent due to an adverse event and had originally been included in the “Discontinued due to Other Reasons” category.

**Table 5 Efficacy outcomes through Week 48, APV30001**

	GW908+ABC+3TC (n=166)	Nelfinavir+ABC+3TC (n=83)
<b>Responder<sup>1</sup></b>	66% (57%)	52% (42%)
<b>Virologic failure</b>	19%	32%
Never <400 c/mL	3%	13%
Rebound	16%	19%
<b>Death</b>	0	2%
<b>Clinical progression</b>	1%	1%
<b>Discontinued due to AEs</b>	4%	2%
<b>Discontinued due to other reasons<sup>2</sup></b>	10%	10%

1. Defined as achieving and maintaining HIV-1 RNA <400 c/mL (<50 c/mL).

2. Includes consent withdrawn, lost to follow-up, missing data, and other reasons.

There was a slightly greater mean change from baseline in HIV-1 RNA in the GW908 arm, -2.17 log<sub>10</sub> c/mL versus -1.9 log<sub>10</sub> c/mL in the NFV arm; the difference was not statistically significant (p=0.8).

An analysis of the proportion of patients with HIV-1 RNA <400 c/mL based on randomization strata of screening HIV RNA demonstrated that for patients with low (<10,000 c/mL) and high baseline HIV-1 RNA values (>100,000 c/mL) GW908 appeared more effective than NFV (see Table 6).

**Table 6 Proportion with HIV RNA <400 c/mL by screening HIV-1 RNA**

	GW908+ABC+3TC	Nelfinavir+ABC+3TC
<b>1,000-10,000 c/mL</b>	73% (11/15)	50% (4/8)
<b>&gt;10,000-100,000 c/mL</b>	64% (50/78)	68% (26/38)
<b>&gt;100,000 c/mL</b>	67% (49/73)	35% (13/37)

## CLINICAL REVIEW

### Clinical Review Section

Among patients with very high baseline viral loads (>500,000 c/mL), a post-hoc analysis showed that those treated with GW908 had higher numerical responses, 61% (14/23) versus 31% (5/16). However, the overall number of patients in this category was small and therefore, caution should be used in concluding that GW908 represents a preferred choice in this subgroup of patients.

#### Immunologic Outcomes

The mean change from baseline in CD4 cell counts was similar: +139 and +136 cells/mm<sup>3</sup> in the GW908 and NFV arms, respectively. The median change was +201 cells/mm<sup>3</sup> in the GW908 arm and +216 cells/mm<sup>3</sup> in the NFV arm.

#### HIV-1 Disease Progression

According to the applicant, seven patients in the GW908 and two in the NFV group experienced HIV disease progression (CDC Class C event) or death.

In the GW908 arm, the progression events listed Kaposi's sarcoma (n=1), CMV retinitis (n=1), histoplasmosis (n=1), toxoplasmosis of the brain (n=2), cryptococcus (n=1) esophageal candidiasis (n=1), Mycobacterium tuberculosis (n=1), pneumocystis carinii pneumonia (n=1), and HIV wasting syndrome (n=1).

**Comment: Six of the GW908 patients were determined not to have confirmed disease progression. Specifically, these patients experienced their events early (usually within the first weeks) and more often experienced recurrences of previous events with corresponding increases in CD4 cell counts. Therefore, these events were more likely due to immune reconstitution than being new diagnoses.**

The one patient in the GW908 arm with confirmed disease progression was diagnosed with oropharyngeal candidiasis at week 24 of the study. The disease progression events in the NFV arm were a Mycobacterium avium complex diagnosed at week 12 and one death due to disseminated histoplasmosis.

#### Genotypic/Phenotypic Resistance

Virologic failure was defined as either two or more consecutive samples with HIV RNA  $\geq$ 1000 c/mL at week 12 or beyond after achieving an HIV RNA <400 c/mL or never achieving HIV RNA <400 c/mL by week 12.

None of the baseline HIV-1 isolates from patients with virologic failure (n=30) contained mutations associated with amprenavir resistance or other protease inhibitors (PIs). Genotypic analysis of on-therapy HIV-1 isolates from 29 patients with virologic failure on GW908 showed that five had amprenavir-resistance-associated mutations: I54L/M, I54L+L33F, V32I+I47V, or M46I+I47V. Phenotypic analysis demonstrated that two of these patients exhibited 5.7 to 7.2-fold reduced susceptibility to amprenavir.