

## CLINICAL REVIEW

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Mutations D30N, N88D alone or in combination with L90M confer resistance to NFV. Nine of 27 patients with virologic failure in the NFV arm had one or more of these mutations compared to none in the GW908 arm.

#### Subgroup Analyses

Black and Hispanic patients responded slightly less well to GW908 than Whites: 58% and 61% versus 76%. Females and males treated with GW908 responded similarly. There was no treatment difference based on age. Patients co-infected with chronic hepatitis B responded well to GW908+3TC+ABC (75% [6/8]), which may have been due to use of 3TC which is an approved therapy for HBV, but numbers are very small. Patients with chronic hepatitis C virus infection responded less well, 48% versus 66%, than patients not co-infected.

#### C.1.b Study APV30002

Study APV30002 was entitled "A randomized, open-label, study that compared the safety and antiviral efficacy of Lexiva/ritonavir once daily to NFV twice daily when used in combination with abacavir and lamivudine BID for 48 weeks in antiretroviral therapy naïve HIV-1 infected subjects."

This study was conducted at 101 sites in the United States, Canada, Spain, Italy, France, Germany, Poland, Austria, Israel, Portugal, Switzerland, the United Kingdom, Australia, South Africa, Belgium, Greece, Hungary, Ireland, and Latvia between November 2000 and August 2002.

#### Objectives

The primary objective was to compare the magnitude and durability of the antiviral response between GW908/ritonavir administered once daily compared to NFV administered twice daily.

Secondary objectives were to compare:

- Safety, tolerance, and antiviral response after 48 weeks of therapy
- Immunologic responses
- Development of resistance

#### Design

This was a randomized, open-label, two-group study in HIV-1 infected antiretroviral-naïve subjects (defined as having had less than 4 weeks [28 days] therapy with any NRTI and no previous therapy with any NNRTI or PI). Patients participated in a Screening period (up to Day -28), a randomized treatment period (Day 1 until the last subject enrolled completed the 48 Week visit) and a follow-up period (conducted 4 weeks after discontinuation from the study). Six hundred sixty patients were randomized to one of the following treatment groups in a 1:1 manner

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and stratified by screening plasma HIV-1 RNA (1000-10,000 c/mL; >10,000-100,000 c/mL; or >100,000 c/mL):

Group 1: GW908 1400mg + ritonavir 200mg QD + ABC 300mg BID + 3TC 150mg BID  
Group 2: NFV 1250mg BID + ABC 300mg BID + 3TC 150mg BID.

Treatment was for 48 weeks. Beginning at week 12, patients with evidence of virologic failure (HIV RNA >1000 c/mL confirmed within 4 weeks) whose virus remained susceptible to their randomized PI could remain on their PI and construct a new background regimen. If the patient's virus was resistant to their randomized PI, the patient could switch PIs. If no regimen could be constructed, the patient was discontinued from the study.

Patients were to remain on study until the last subject enrolled completed 48 weeks. A roll over protocol, APV30005, was available for GW908 subjects who completed 48 weeks or more. Subjects enrolled in APV30005 would receive GW908 is approved. Subjects who experienced virological failure to NFV and switched to GW908 were also allowed to rollover into APV30005.

Tablet Variants A and B were used in this study.

### Demographics and Disposition

Eligible patients included males and females 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  $\geq$ 1000 copies/mL. Female subjects must have been of: a non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including post-menopausal status) or 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 7.

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**Table 7 Demographics and disease characteristics, APV30002**

	GW908/r+ABC+3TC (n=322)	Nelfinavir+ABC+3TC (n=327)
<b>Age</b>		
<b>Median (range)</b>	36 (18, 69)	36 (18, 68)
<b>Gender</b>		
<b>Male</b>	70%	76%
<b>Female</b>	30%	24%
<b>Race</b>		
<b>White</b>	51%	54%
<b>Black</b>	38%	33%
<b>Asian</b>	2%	2%
<b>American Hispanic</b>	7%	8%
<b>Other</b>	2%	2%
<b>HIV RNA (log<sub>10</sub> c/mL)</b>		
<b>Median (range)</b>	4.78 (2.65-7.29)	4.83
<b>≥1,000-10,000</b>	9%	10%
<b>10,000-100,000</b>	52%	49%
<b>&gt;100,000</b>	39%	41%
<b>CD4 cells/mm<sup>3</sup></b>		
<b>Median (range)</b>	166	177 (1-1055)
<b>CDC Classification</b>		
<b>B</b>	23%	25%
<b>C</b>	21%	22%
<b>Hepatitis C reactive</b>	18%	18%
<b>Hepatitis B reactive</b>	8%	7%

Fifty one and 47 patients in the GW908 and NFV arms, respectively, entered the study with baseline HIV-1 RNA levels >500,000 c/mL.

**Comment:** The demographic and disease characteristics were well matched between study arms and represented a population with moderately advanced disease.

Table 8 presents the applicants' assessment of patient disposition.

**Table 8 Patient disposition through 48 weeks (applicant), APV30002**

	GW908/r+ABC+3TC	Nelfinavir+ABC+3TC
<b>Randomized</b>	322	327
<b>Received at least one dose of study medication</b>	322	325
<b>Completed 48 weeks on randomized PI</b>	231 (72%)	242 (74%)
<b>Discontinued randomized PI</b>	91 (28%)	85 (26%)
<b>-Adverse event</b>	28 (9%)	16 (5%)
<b>-Consent withdrawn</b>	16 (5%)	11 (3%)
<b>-Lost to follow-up</b>	24 (7%)	15 (5%)
<b>-Met switch criteria*</b>	1 (<1%)	27 (8%)
<b>-Protocol violation</b>	4 (1%)	16 (19%)
<b>-Other</b>	18 (6%)	12 (4%)

\* Defined as consecutive plasma HIV-1 RNA >1000 c/mL on or after week 12.

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More subjects prematurely discontinued due to adverse events in the GW908/ritonavir group than in the NFV group. In the GW433908/ritonavir arm these were primarily gastrointestinal events (nausea, vomiting diarrhea, elevated AST/SLT). There was no specific pattern to the timing of these events. ABC HSR accounted for eight discontinuations.

Substantially more patients discontinued from the NFV arm due to virologic failure.

Review of individuals who discontinued due to consent withdrawal yielded six patients in the GW908/ritonavir and seven in the NFV arm who were experiencing adverse events reasonably attributable to study treatment at the time they withdrew consent. These events included diarrhea, rash, increased lipase, increased abdominal girth, increased AST/ALT, and depression in the NFV arm, and pruritis, headache, abdominal pain, diarrhea, increased ALT/AST, and chills and fever were the events in the GW908/ritonavir arm. Therefore, discontinuations due to adverse events should be 34 (11%) for GW908/ritonavir and 22 (7%) for NFV. However, regardless of the reason for discontinuation, patients who discontinued were classified as treatment failures in the efficacy analyses.

#### Endpoints, Analyses and Results

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

The primary endpoint was the proportion of patients with HIV-1 RNA <400 c/mL at 48 weeks. The primary analysis was to demonstrate the non-inferiority of GW908/ritonavir to NFV with respect to the proportion of subjects achieving a plasma HIV-1 RNA level <400 copies at Week 48. Using a margin of 12% to assess non-inferiority, and assuming a 50% success rate in each treatment arm, the applicant calculated that the number of patients enrolled would provide approximately 85% power to test this at the 2.5% significance level. If the 95% confidence interval lies above -12%, the applicant would conclude that GW908/ritonavir is non-inferior to NFV.

As in study APV30001, 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).

Secondary endpoints included:

- Proportion of subjects with plasma HIV-1 RNA levels below 50 c/mL at 48 weeks
- Measured values and AAUCMB in plasma HIV-1 RNA
- Measured values and AAUCMB in CD4+ cell counts
- Progressions of HIV disease as measured by CDC Classifications and deaths
- Genotypic/phenotypic analysis of selected viral isolates

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Table 9 reflects the overall results of the study and contains the data that will be included in the labeling. In Table 9, the category “Discontinued due to Adverse Events” reflects the re-categorization of seven GW908 and six NFV patients who withdrew consent due to an adverse event and had originally been included in the “Discontinued due to Other Reasons” category.

**Table 9 Efficacy outcomes through Week 48, APV30002**

	GW908/r+ABC+3TC (n=322)	Nelfinavir+ABC+3TC (n=327)
<b>Responder<sup>1</sup></b>	69% (58%)	68% (55%)
<b>Virologic failure</b>	6%	16%
Never <400 c/mL	1%	8%
Rebound	5%	8%
<b>Discontinued due to AEs</b>	9%	6%
<b>Death</b>	1%	0
<b>Discontinued due to other reasons<sup>2</sup></b>	15%	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.

Based on the lower bound of the 95% confidence limits for the primary endpoint, -8.2%, the conclusion that GW908/ritonavir is non-inferior to NFV is supported.

There was no difference in mean change from baseline in HIV-1 RNA between arms: -2.26 log<sub>10</sub> c/mL in the GW908 arm and -2.32 log<sub>10</sub> c/mL in the NFV arm (p=0.4).

The analysis of the proportion of patients with HIV-1 RNA <400 c/mL based on screening HIV-1 RNA yielded no significant differences between treatment arms for any strata (see Table 10).

**Table 10 Proportion with HIV-1 RNA <400 c/mL by screening HIV-1 RNA**

	GW908/r+ABC+3TC	Nelfinavir+ABC+3TC
<b>1,000-10,000 c/mL</b>	76% (23/30)	76% (25/33)
<b>&gt;10,000-100,000 c/mL</b>	70% (118/167)	72% (116/161)
<b>&gt;100,000 c/mL</b>	66% (82/125)	64% (84/133)

Among patients with very high baseline viral loads (>500,000 c/mL), those treated with GW908 had higher numerical responses, 62% (32/51) versus 44% (21/47), but the numbers were small and this difference did not reach statistical significance, p=0.06.

**Comment:** The results of the proportion <400 c/mL analysis by baseline HIV-1 RNA demonstrates generally comparable efficacy between treatment arms. Thus, the results shown above for study APV30001 (Table 6) appear to be spurious and not completely representative of the activity of the NFV-based regimen.

### Immunologic Outcomes

In this study, the mean change from baseline in CD4 cell counts was +137 cells/mm<sup>3</sup> in the GW908/ritonavir arm and +150 cells/mm<sup>3</sup> in the NFV arm. The median change was +203 and +207 cells/mm<sup>3</sup> in the GW9089/ritonavir and NFV arms, respectively.

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#### **HIV-1 Disease Progression**

Progression of HIV disease was measured by CDC Classifications and deaths. Thirty patients, 15 per treatment arm, had events consistent with CDC Classification C events.

In the GW908/ritonavir arm, seven events consistent with progression included new onset Mycobacterium avium complex (day 21 and 33), immunoblastic lymphoma (day 238), Kaposi Sarcoma of the lung (day 45, patient died secondary to sepsis), isopsoriasis (day 197), CMV retinitis (day 49, patient died secondary to Burkitts lymphoma), Pneumocystis carinii pneumonia (day 44). The eight other events occurred early in treatment (prior to day 14), and in most cases the CD4 cell counts were low at the time of event, typically  $<150$  cells/mm<sup>3</sup>.

**Comment: Events that occurred early in the study in patients with low CD4 cell counts suggested a pattern consistent with the syndrome of immune reconstitution.**

#### **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.

Genotypic analysis of baseline-matched on-therapy HIV-1 isolates from 32 patients with virologic failure on GW908 therapy showed that none harbored amprenavir-resistance-associated mutations. Phenotypic analysis demonstrated that all isolates were susceptible to amprenavir.

On therapy HIV-1 isolates from 28 of 54 patients with virologic failure in the NFV arm contained NFV-resistance associated mutations D30N. Gag-pol cleavage site mutation p1/p6 P449L was detected in isolates from one-NFV BID-treated patients.

**Comment: Compared to GW908 alone, co-administration with ritonavir may have increased the genetic barrier to resistance to amprenavir.**

#### **Subgroup Analyses**

In this study, male patients responded better than female patients, 68% versus 42%. Also Hispanic patients responded better than Whites, Blacks and other races. There was no treatment effect by age observed. Patients co-infected with either chronic hepatitis B or C responded less well compared to patients not co-infected. Although all patients received 3TC, there did not appear to be a treatment benefit for patients with chronic hepatitis B virus co-infection.

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#### C.1.c Study APV30003

Study APV30003 was a phase 3, randomized, multicenter, parallel group, open-label, study to compare the efficacy and safety of two dosing regimens of GW908/ritonavir versus Kaletra® (lopinavir/ritonavir, LPV/r, Abbott Laboratories) for 48 weeks in PI experienced adults experiencing virological failure.

The study was conducted at 103 sites in the US, Australia, Belgium, Canada, Chile, France, Germany, Portugal, Puerto Rico, Spain, Switzerland, and the United Kingdom between May 2001 and .

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#### Objectives

The primary objective was to test the non-inferiority of two different dosage regimens of GW908/ritonavir versus LPV/r (as measured by average area under the curve minus baseline [AAUCMB] in plasma HIV-1 RNA) at 48 weeks.

The secondary objectives of the study were to compare:

- Safety and tolerability
- Proportions of patients with HIV-1 RNA <400 and <50 c/mL
- Immunologic responses.
- Viral resistance patterns at baseline and those which emerge in subjects with virologic failure, and to correlate these patterns with treatment outcome.

#### Design

This was a randomized, open-label, parallel group, three-arm study. A total of 315 PI-experienced subjects with documented PI resistance (based on genotypic analysis) and for whom an active background regimen of two NRTIs could be constructed were enrolled, and randomized 1:1:1 to 48 weeks of therapy with:

- Group 1: GW908 1400mg QD + ritonavir 200mg QD + 2 NRTIs
- Group 2: GW908 700mg BID + ritonavir 100mg BID + 2 NRTIs
- Group 3: Kaletra® (lopinavir 400mg BID + ritonavir 100mg) BID + 2 NRTIs

Patients were stratified according to PI experience (1 or 2 prior PIs) and baseline HIV-1 RNA (5,000 to 10,000 c/mL, >10,000-100,000 c/mL, or >100,000 c/mL).

The study was initiated with Tablet Variants A and B with all patients subsequently switched to Table Variant C.

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#### Patient Demographics and Disease Characteristics

Males and females  $\geq 13$  years of age were eligible if they had a screening plasma HIV-1 RNA  $\geq 1000$  c/mL while receiving antiviral therapy including a PI. Patients had to have previous experience with one or two PI's, either as a single PI, or as part of a pharmacokinetically-enhanced regimen (ritonavir 200mg or less) and previous experience with NNRTIs. Patients had to have genotypic evidence of resistance to one or more PIs. Female subjects were to be of non-childbearing potential or, if of child-bearing potential, have a negative pregnancy test at baseline and either abstain from sexual intercourse or utilize a double-barrier method of contraception during the study. Subjects were not eligible to enroll if they had received prior treatment with lopinavir/ritonavir or amprenavir.

The demographic and disease characteristics of study patients are presented in Table 11.

**Table 11 Demographic and disease characteristics, APV30003**

	GW908/r QD (n=105)	GW908/r BID (n=107)	LPV/r (n=103)
<b>Age</b>			
<b>Median (range)</b>	42 (25, 59)	40 (24, 72)	41 (29, 70)
<b>Gender</b>			
<b>Male</b>	82%	87%	83%
<b>Female</b>	18%	13%	17%
<b>Race</b>			
<b>White</b>	73%	70%	57%
<b>Black</b>	19%	21%	32%
<b>Asian</b>	7%	8%	11%
<b>American Hispanic</b>	<1%	<1%	0
<b>Other</b>			
<b>HIV RNA (log<sub>10</sub> c/mL)</b>			
<b>Median (range)</b>	4.19	4.13	4.13 (1.69-6.41)
<b><math>\geq 1,000</math>-10,000</b>	39%	38%	40%
<b>10,000-100,000</b>	46%	45%	46%
<b>&gt;100,000</b>	15%	17%	15%
<b>CD4 cells/mm<sup>3</sup></b>			
<b>Median (range)</b>	308 (2-1171)	316	274
<b>CDC Classification</b>			
<b>B</b>	29%	27%	30%
<b>C</b>	34%	32%	34%
<b>Hepatitis C reactive</b>	15%	15%	17%
<b>Hepatitis B reactive</b>	7%	4%	5%

The median duration of previous PI was similar across treatment arms, 140 weeks. Higher proportions of GW908/ritonavir once and twice daily patients had received  $\geq 2$  PIs: 57% and 49%, respectively, compared to 40% of LPV/r patients. The NRTI combinations used were similar across the three treatment groups; again the duration and proportion who had received  $\geq 3$  prior NRTIs were greater in the two GW908/ritonavir arms. There were no differences for duration or number of previous NNRTIs.

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More patients in the LPV/r arm were Black; the relevance of this imbalance is not known. Approximately one-third of patients entered with a history of CDC Class C disease, 12% had very high baseline viral load (>100,000 c/mL), but most patients also had reasonably high baseline CD4 cell count (~300 cells/mm<sup>3</sup>).

**Comment: The differences in patient characteristics and history of previous antiretroviral therapy were not expected to impact comparability of the treatment groups. In general, the population, although previously treated, did not have significantly advanced HIV-1 disease; these patients had other treatment options available if they had not enroll in the study.**

The disposition of study patients is presented in Table 12.

**Table 12 Patient disposition through 48 weeks (applicant), APV30003**

	GW908/r QD	GW908/r BID	LPV/r
<b>N randomized</b>	107	107	106
<b>N treated</b>	105	107	103
<b>N (%) prematurely discontinued</b>	25 (24%)	28 (26%)	22 (21%)
<b>DC reasons n (%)</b>			
Adverse event	2 (2%)	5 (5%)	7 (7%)
Consent withdrawn	3 (3%)	0	2 (2%)
Virologic failure*	12 (11%)	12 (11%)	1 (<1%)
Lost to follow-up	6 (6%)	9 (8%)	8 (8%)
Protocol violation	1 (<1%)	1 (<1%)	0
Other	1 (<1%)	1 (<1%)	5 (5%)

Source: Table 14.4

\*Defined as never achieved viral load suppression by week 48, plasma HIV-1 RNA rebound, or premature discontinuation due protocol defined virologic failure.

The patient discontinued for protocol violation in the once daily arm had two violations: no assessments past entry day 1 and insufficient RTI background based on genotyping. The patient in the twice daily arm was discontinued for no assessments past entry day 1 and non-adherence.

Two LPV/r patients were experiencing adverse events at the time they withdrew their consent. : rash and dyspnea and nausea and fatigue. The category "Other" included non-compliance, patient refusal to return for follow-up visits, and patient decision.

### Endpoints, Analyses and Results

The primary analysis population is the intent-to-treat defined as those patients who were randomized and received at least one dose of study medication.

The primary study endpoint was time-averaged change from baseline in (AAUCMB) in plasma HIV RNA at 48 weeks. The applicant proposed to conclude that either GW908/ritonavir regimen was non-inferior to LPV/r if the analysis demonstrated that there was less than a 0.5 log<sub>10</sub> c/mL difference. The applicant's power statement read: to provide approximately 90% power to perform each of these tests at the 1.25% significance level (that is by using two-sided 97.5%

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confidence intervals to assess non-inferiority), assuming a standard deviation in plasma HIV-1 RNA of 0.85 log<sub>10</sub> copies/mL, 72 subjects are required in each arm. This has been increased to a minimum of 82 subjects to adjust for subjects discontinuing prematurely. The width of the confidence intervals accounts for the multiple comparisons; the combined significance level of the two tests will be no more than 2.5%.

The AAUCMB analysis demonstrated that both GW908/ritonavir regimens were inferior to LPV/r. Specifically, although the GW908/ritonavir arms produced similar mean changes from baseline in HIV-1 RNA of -1.38 log<sub>10</sub> c/mL for once daily and -1.39 log<sub>10</sub> c/mL for twice daily, LPV/r produced a mean -1.66 log<sub>10</sub> c/mL reduction of HIV-1 RNA from baseline. The lower bound of the 95% confidence intervals for the difference between GW908/ritonavir once daily versus LPV/r was 0.01 (p=0.04), and for GW908/ritonavir twice daily versus LPV/r it was 0 (p=0.05).

Secondary efficacy endpoints included the comparisons of changes from baseline in CD4 cell counts, the proportions of patients with HIV-1 RNA <400 c/mL and 50 c/mL, and analysis of genotypic/phenotypic resistance.

LPV/r and GW908/ritonavir twice daily produced numerically similar proportions of patients with HIV-1 RNA <400 and 50 c/mL. GW908/ritonavir once daily was, on all endpoints, inferior to both GW908/ritonavir twice daily and LPV/r (see Table 13). The table considers the reclassification of patients as described above.

**Table 13 Efficacy outcomes through Week 48, APV30003**

	GW908/r QD n=105	GW908/r BID n=107	LPV/r BID N=103
<b>Responder<sup>1</sup></b>	50% (37%)	58% (46%)	61% (50%)
<b>Virologic failure<sup>2</sup></b>	33%	23%	28%
<b>Never suppressed</b>	16%	12%	9%
<b>Rebound</b>	17%	11%	19%
<b>Discontinued due to AEs</b>	1%	1%	8%
<b>Death</b>	0%	1%	0%
<b>Discontinued due to other reasons<sup>3</sup></b>	16%	17%	3%

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

2. Defined as plasma HIV-1 RNA >10,000 copies/mL or above baseline on two consecutive occasions after initial suppression (below 400 copies/mL), or less than a 0.7 log<sub>10</sub> reduction in plasma HIV-1 RNA by Week 16.

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

The lower bound of the 95% confidence limit for the proportion with HIV-1 RNA <400 c/mL between GW908/ritonavir once daily and LPV/r was -25%, supporting the conclusion that GW908/ritonavir once daily was significantly less efficacious than LPV/r. The lower bound of the 95% confidence interval for the difference between GW908/ritonavir twice daily and LPV/r was -16.6%, demonstrating that twice daily GW908/ritonavir is better than once daily in PI-experienced patients, but still less effective than LPV/r.

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The reason for the significant underperformance of the GW908/ritonavir once daily arm might have been due to lower plasma amprenavir exposure and  $C_{min}$  with GW908/ritonavir once daily compared to GW908/ritonavir twice daily.

Analysis based on the HIV-1 RNA randomization strata demonstrated that for patients with high baseline viral load ( $>100,000$  c/mL) treatment with LPV/r produced the highest proportion with HIV-1 RNA  $<400$  c/mL (see Table 14). Caution should be used when interpreting the results for these patients as the number in this category are small.

**Table 14 Proportion with HIV-1 RNA  $<400$  c/mL by screening HIV-1 RNA**

	GW908/r QD n=105	GW908/r BID n=107	LPV/r BID n=103
1,000-10,000 c/mL	61% (25/41)	76% (31/41)	71% (29/41)
$>10,000$ -100,000 c/mL	46% (22/48)	54% (26/48)	55% (26/47)
$>100,000$ c/mL	31% (5/16)	28% (5/18)	53% (8/15)

### Immunologic Outcomes

Consistent with the virologic results above, treatment with LPV/r resulted in higher mean increases from baseline in CD4 cell counts: +64 compared to +50 cells/mm<sup>3</sup> in the twice daily and +53 cells/mm<sup>3</sup> in the once daily GW908/ritonavir arms. Similarly, median increases were higher in the LPV/r arm compared to the GW908/ritonavir once and twice daily arms, +91, +81, and +61 cells/mm<sup>3</sup>.

### Resistance Outcomes

Genotypic analysis showed that at baseline HIV-1 from 8% of patients contained primary PI - resistance mutations consisting of: D30N, M46I/L, I54V, V82A/F/TS, N88D, I84V, and L90M. In addition, V32I, G48V, I54L/M, and N88S mutations were also present in some baseline HIV-1 isolates. V32I, I50V, I54L/M and I84V mutations are known to convey resistance to amprenavir. The I54L and V32I mutations were present in baseline HIV-1 isolates from 2/107 and 1/107 patients randomized to 908/ritonavir twice daily, respectively. The I54V mutation was present in 12/105 patients receiving GW908/ritonavir once daily and 11/107 patients in GW908/ritonavir twice daily group. The I84V mutation was present at baseline in 8/105 patients receiving GW908/ritonavir once daily and 8/107 in GW908/ritonavir twice daily group.

Phenotypic analysis showed that baseline HIV-1 isolates from 81/93 and 71/88 patients in the GW908/RTV once and twice daily, respectively, were susceptible to amprenavir in vitro. Baseline HIV-1 isolates from the remaining 12/93 and 17/88 patients exhibited a 2.5- to  $<6$ -fold decreased susceptibility to amprenavir in vitro.

Virologic response was impacted by the presence of certain protease mutations at baseline. Specifically, presence of I54V, I84V and V82A/F/T/S were associated with a lower rate of response with GW908/ritonavir compared to LPV/r (see Table 15).

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**Table 15 Responders at study Week 48 by presence of baseline PI mutations, N(%)**

PI-mutations*	GW908/ritonavir BID (N=88)	LPV/R BID (N=85)
D30N	20/21 (95%)	16/16 (100%)
N88D/S	18/21 (86%)	12/12 (100%)
L90M	16/31 (52%)	17/28 (61%)
M46I/L	11/22 (50%)	12/24 (50%)
V82A/F/T/S	2/9 (22%)	6/17 (35%)
I54V	2/11 (18%)	4/9 (44%)
I84V	1/6 (17%)	2/5 (40%)

\* Most patients had more than one PI mutation at baseline.

Phenotypic analysis data were available for baseline matched on-therapy HIV-1 isolates from 20 virologic failure patients who received GW908/ritonavir once daily and 22 who received GW908/ritonavir twice daily. In the once daily group isolates from 11/20 virologic failure patients demonstrated a median shift in susceptibility to amprenavir of 0.7 (range 2.6 to 19-fold). Eight of the 11 had one or more mutations associated with amprenavir resistance: V32I, M46I/L, I47V, I50V, I54L/M, and I84V. Similarly, in the twice daily group, 17/29 isolates from virologic failure patients exhibited a median shift of susceptibility of 1.9 (range 0.2-14-fold), and 15 isolates contained one or more amprenavir -resistance-associated mutations.

**Comment: The resistance pattern for GW908 was expected and comparable to that of Agenerase. Presence of the I54V, I84V and V82/A/F/T/S mutations at baseline translated into lower antiviral response rates in patients treated with GW908/ritonavir. These data suggest that baseline genotyping data has utility in predicting antiviral responses and should assist clinicians in making a choice about initiating GW908 in PI-experienced patients.**

#### Assessment of Study APV30003

The study results demonstrate that, for the primary endpoint (AAUCMB), both GW908/ritonavir arms were inferior to LPV/r. For the secondary endpoints of proportion of patients with HIV-1 RNA <400 c/mL and <50 c/mL, GW908/ritonavir and LPV/r produced antiviral activity that was numerically similar, but LPV/r produced greater increases in CD4 cell counts. This study was powered based on the endpoint of AAUCMB and not on proportion with HIV-1 RNA <400 c/mL. Thus, the study was not large enough to demonstrate that Lexiva™ is a clinically equivalent substitute for Kaletra.

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To support a conclusion that GW908/ritonavir twice daily is equivalent to LPV/r, a larger study, adequately powered to detect differences in the proportion of patients with HIV-1 RNA <400 c/mL or 50 c/mL, would be necessary.

GW908/ritonavir once daily produced significantly inferior activity compared to both the GW908/ritonavir twice daily and LPV/r arms, and will not be recommended for use in this population.

#### D. Efficacy Conclusions

In treatment naïve patients (Studies APV30001 and APV30002) GW908 1400 mg twice daily and 1400 mg plus 200 mg of ritonavir once daily, with abacavir and lamivudine, produced similar efficacy as evidenced by the proportions of patients with HIV-1 RNA <400 (64% and 60%), <50 c/mL, (54% and 51%), median change from baseline in HIV-1 RNA (-2.17 and -2.26  $\log_{10}$  c/mL), and mean change in CD4 cell counts (+129 and +117 cells/mm<sup>3</sup>). In both studies, more patients achieved and maintained virologic suppression on GW908. Also, co-administration of ritonavir appeared to delay the emergence of resistance to GW908.

In study APV30001, the regimen of Lexiva™+ABC+3TC was active and produced clinically relevant antiviral responses consistent with other first-line PI-based regimens. The results suggested that this regimen could produce superior antiviral efficacy compared to NFV+ABC+3TC. However, on close scrutiny, this may not be the most appropriate conclusion to reach. For example, although a higher proportion of patients in the GW908 arm achieved HIV-1 RNA <400 c/mL, both regimens produced similar reductions from baseline in HIV-1 RNA, -2.0  $\log_{10}$  c/mL.

Also, the efficacy of the NFV arm was inconsistent with previous studies in which NFV was administered with two NRTIs to treatment naïve patients. In those studies, typically more than 60% of patients achieve HIV-1 RNA <400 c/mL. Factors such as differences in demographic and baseline disease characteristics, extent of exposure to NFV, and sampling variability around observed effects were evaluated in study APV30001, but none were found to have led to the differences.

It is interesting to note the differential efficacy produced by the NFV arm in studies APV30001 and APV30002. The disease and demographic characteristics of the NFV patient populations in studies APV30001 and APV30002 were well matched, but in study APV30001 more patients in the NFV arm failed to complete the study compared to study APV30002 (60% versus 43%), which resulted in those patients being classified as treatment failures in the analyses of efficacy. Also, the primary endpoint on which each study was powered was different: AAUCMB in study APV30001 versus proportion <400 c/mL in study APV30002. Thus, the assessment of comparative antiviral efficacy in study APV30001 was based on 83 NFV-treated patients compared to 327 in study APV30002. These differences may have introduced some variability as well as the fact that the studies were open-label which could also have introduced other biases.

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In summary, the GW908 arm produced antiviral and immunologic efficacy generally comparable to an established comparator. However, the comparison to the NFV arm of study APV30001 must be carefully scrutinized as they are not typical of the expected outcome of a NFV plus two NRTI regimen in treatment naïve patients. The results of the NFV arm in study APV30002 were more expected. And therefore, the results of study APV30001 should be placed in context alongside the results of study APV30002, which suggested comparability of GW908 and NFV.

The results from these two studies support the conclusion that GW908 with or without ritonavir represents acceptable methods for administration of Lexiva™ to treatment naïve patients.

Study APV30003 was conducted in patients who had failed previous PI-based regimens. Treatment with GW908/ritonavir and LPV/r twice daily resulted in numerically similar proportion of patients achieving HIV-1 RNA <400 c/mL, but lower mean increase in CD4 cells and a smaller reduction from baseline in HIV-1 RNA. GW908/ritonavir once daily, however, produced significantly inferior efficacy than either GW908/ritonavir twice daily or LPV/r, and will not be recommended for use in this patient population.

Mutations conveying resistance to GW908 are the same as those conveying resistance to amprenavir, i.e., one or more mutations in the protease gene resulting in amino acid substitutions at positions M46L, I47V, I50V, and I84V. Co-administration of ritonavir in a moderate number of treatment naïve patients (APV30002) appeared to protect against the emergence of resistance compared to the study in which ritonavir was not used (APV30001). In PI-experienced patients, the presence of I54V, I84V and V82/A/F/T/S was associated with treatment failure.

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#### **VII. Integrated Review of Safety**

##### **A. Brief Statement of Conclusions**

In HIV trials adverse event data were collected on the entire study drug regimen, which can sometimes make assessment of the relationship of a particular adverse event to a particular drug challenging.

Lexiva™ (GW908, fosamprenavir) is nearly 99% converted to an active compound, amprenavir, which is also the active component of Agenerase®. Amprenavir is a protease inhibitor with a well described and characterized adverse event profile when used with and without ritonavir as a component of multi-drug antiretroviral regimen.

Pre-clinical animal studies demonstrated gastrointestinal toxicities (vomiting, soft and watery stools), increased cholesterol, decreased triglycerides, and increased serum AST and ALT. The most common clinical adverse events and laboratory abnormalities associated with amprenavir are diarrhea, nausea, vomiting, fatigue, headache, rash, and peripheral/oral paresthesias. When co-administered with ritonavir, the frequency of diarrhea increases as does hypertriglyceridemia and hyperglycemia.

The most common events reported in patients treated with GW908 (with and without ritonavir) included diarrhea, nausea, vomiting, headache, fatigue, rash, pruritis, oral and peripheral paresthesia, and mood disorders/depression. Common laboratory abnormalities included hepatic transaminitis, increased cholesterol, triglycerides, and glucose levels. Most events were considered mild to moderate in severity. All of these events were predictable and expected based on preclinical data and data from clinical trials with amprenavir. Overall, addition of ritonavir led to an increase in the frequency and severity of diarrhea, vomiting, and triglyceride and cholesterol level increases.

These events are comparable to the events reported among patients receiving Agenerase. No new types of adverse clinical or laboratory events were identified that could have been related to any remaining GW908 that is not converted to amprenavir.

All the patients in studies APV30001 and APV30002 received abacavir (ABC) as a component of their background regimen. Hypersensitivity reaction (rash, fever, and constitutional symptoms) to abacavir is a well-characterized toxicity reported to occur in between 3 and 9% of recipients. Abacavir hypersensitivity reaction (ABC HSR) was reported in a total of 9% of patients in the two studies, with 4% being of Grade 3 or 4 severity. The frequency and severity was generally comparable between treatment arms.

##### **B. Description of Patient Exposure**

The NDA contains safety data on over 2000 HIV-1 infected patients exposed to GW908 in short-term clinical pharmacology and long-term treatment studies. Data on 770 HIV-1 infected patients who received GW908 alone or in combination with ritonavir in the three pivotal clinical studies was submitted in the NDA. Exposure to GW908 in these studies at the proposed

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marketing doses was a median of 350 days (range 1-560 days). Additional safety data was submitted from ongoing IND (n=754) and non-IND (n=270) studies.

A safety-update was submitted April 18, 2003 (cut off of February 7, 2003), as well as periodic Serious Adverse Event reports from ongoing studies.

#### **C. Methods and Specific Findings of Safety Review**

All clinical pharmacology studies were reviewed for their contribution to the assessment of GW908's safety. Headache, rash, diarrhea and loose stools, pruritis, fatigue, nausea, and oral/perioral numbness were the most commonly reported events in healthy subjects receiving GW908 with or without ritonavir. These events were expected as they are the most common events reported to be related to amprenavir. Also, their frequencies were comparable to previous amprenavir studies. Thus, they provided a reasonable assessment of events possibly or probably attributable to delivery of amprenavir as GW908.

##### **C.1. Deaths**

A total of 11 patients died: seven of whom received GW908.

Causes of death among GW908 recipients included sepsis secondary to Kaposi Sarcoma of the lung, cardiac failure/status asthmaticus, myocardial infarction, suicide, sepsis, diffuse B-cell lymphoma, and an intracranial bleed from a congenital arterio-venous malformation.

A relationship between GW908 and the death due to myocardial infarction could not be ruled out. The patient was a 44-year old male initially treated with GW908/ritonavir in study APV30002. He had a history of smoking and family history of hyperlipidemia. Following completion of study APV30002, he started GW908/ritonavir once daily in study APV30005, the long term roll over study. At entry, his cholesterol, LDL and HDL were normal and his triglycerides were mildly elevated. After approximately four months, his cholesterol had increased >2-fold, LDL increased nearly 3-fold, and triglycerides increased 1.6-fold. Approximately 19 months later the patient presented to an emergency room with chest pain, was diagnosed with a myocardial infarction and died four days later.

A relationship between GW908 and the death due to suicide could also not be ruled out. This was a 45-year old male who received GW908/ritonavir once daily in the open label study (APV30005). After approximately four months, he experienced worsening depression, and committed suicide by ingesting a large number of unknown pills.

##### **C.2. Discontinuations Due to Adverse Events**

Discontinuations occurred with similar frequency across all arms of the three pivotal efficacy studies. Overall, 12% (85/700) of patients who received GW908 experienced adverse events that led to discontinuation of one or more study drugs or complete discontinuation from a study. Of

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these there was a reasonable probability that exposure to GW908 led to approximately 6% of discontinuations. The frequency of discontinuations was generally similar across all study arms.

The most common adverse events leading to discontinuation of GW908 included diarrhea, abdominal pain, nausea, vomiting, dyspepsia, dehydration, and Grade 4 AST/ALT elevations.

Abacavir hypersensitivity reaction (ABC HSR) was the most common reason for discontinuations from both treatment arms in studies APV30001 and APV30002, with equal distribution between treatment arms. One patient in the GW908 arm of study APV30002 discontinued due to ABC HSR induced Stevens-Johnson Syndrome. Six patients discontinued from the studies, but the majority of patients were able to substitute another approved NRTI for ABC and continue.

Two patients in other studies sponsored by the applicant discontinued GW908 therapy due to adverse events related to lipodystrophy and hepatic transaminitis.

### C.3. Serious Adverse Events

Serious events possibly or probably attributable to GW908 included hepatic transaminitis, depression/mood alterations, and attempted suicide. Each event occurred in <1% of patients. The most commonly reported serious adverse event overall was ABC HSR, with one case associated with Stevens-Johnson Syndrome.

### C.4. General Clinical Adverse Events

The adverse events listed in the tables were selected based on the known profile of amprenavir. However, all reported adverse events were reviewed in order to assess the possible occurrence of new events that might be related to amprenavir delivered as GW908; none were identified. In general, adverse events were of mild or moderate severity.

**Table 16 Selected clinical adverse events of all grades, regardless of relationship to study drug, reported in  $\geq 5\%$  of patients (%).**

EVENT	APV30001		APV30002		APV30003		
	GW908 BID (N=166)	NFV BID (N=83)	GW908/r QD (N=322)	NFV BID (N=327)	GW/r QD (N=105)	GW/r BID (N=107)	LPV/r (N=103)
Diarrhea <sup>1</sup>	34	63	52	72	31	38	47
Nausea	39	24	37	27	25	20	31
Vomiting	16	17	20	13	21	10	17
Abdominal pain	5	8	11	11	9	11	9
Headache <sup>2</sup>	19	20	21	27	11	27	20
Fatigue	10	7	18	13	14	9	14
Rash <sup>3</sup>	35	19	17	21	14	9	22
Pruritis	7	11	7	9	9	8	3
Paresthesia, oral	2	0	10	<1	6	<1	0
Paresthesia, peripheral	4	1	2	4	7	4	6
Depressive/mood disorders	8	8	8	6	14	11	10

1. Includes: Diarrhea NOS, loose stools, watery stools.

2. Includes Headache NOS, Headache NOS aggravated, and Migraine NOS

3. Includes: Rash NOS, papular rash, erythematous rash, maculo-papular rash, and Stevens-Johnson Syndrome.

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GW908's clinical adverse event profile was as expected based on data from Agenerase studies.

With the exception of diarrhea in the once daily arm of study APV30002, the addition of ritonavir did not lead to an apparent increase in clinical adverse events. However, when the severity of adverse events are considered, reports of moderate to severe diarrhea were increased from 5% to 10-13% in patients who received GW908/ritonavir.

When compared to previously reported rates of treatment emergent adverse events seen in trials with amprenavir as Agenerase®, taste disturbance and vomiting were reported with less frequency by patients who received GW908. This may be due to the non-aqueous liquid formulation of Agenerase, the higher pill burden (16 capsules/day of Agenerase vs. 2 per day of GW908) and the high vitamin E concentration in Agenerase, which is not present in GW908.

In studies of Agenerase administered with ritonavir, twice daily dosing was associated with lower frequencies of all of the adverse events listed in Table 15. Co-administration of GW908/ritonavir twice daily produced somewhat less nausea, vomiting, fatigue, rash, and peripheral paresthesia compared to GW908/ritonavir once daily. Thus, it appears that consistent with the Agenerase data, twice daily GW908/ritonavir may be better tolerated than once daily administration.

Treatment emergent rashes not due to ABC HSR were generally maculopapular some with pruritis, Grade 1 or 2 in severity with a median time to onset of 11 days and a median duration of 13 days. Most patients with rash not due to ABC HSR continued GW908, and less than 1% of patients discontinued GW908 due to a rash event.

Suicidal ideation/attempt occurred in <1% of patients treated with GW908; similar to the frequency reported in studies with Agenerase.

#### **C.5. Laboratory Abnormalities**

Selected laboratory abnormalities associated with treatment with PIs in general and amprenavir specifically, are presented in Table 17.

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**Table 17 Selected laboratory abnormalities, regardless of relationship to study drug, reported in >5% of patients in the three pivotal GW908 clinical trials.**

PARAMETER	APV30001		APV30002		APV30003		
	GW908 BID (n=166)	NFV BID (n=83)	GW908/r QD (n=322)	NFV BID (n=327)	GW/r QD (n=105)	GW/r BID (n=107)	LPV/r (N=103)
<b>ALT</b>							
All Grades	23	19	27	27	29	30	27
Grade 3-4	6	5	8	8	6	4	4
<b>ALT and/or AST</b>							
All Grades	28	25	34	35	38	38	38
Grades 3-4	6	9	9	10	6	6	4
<b>AST</b>							
All Grades	23	20	23	29	30	26	32
Grades 3-4	6	6	6	7	4	4	2
<b>Serum lipase</b>							
All Grades	20	14	22	20	30	30	28
Grades 3-4	8	4	6	4	5	5	12
<b>Cholesterol</b>							
All Grades	7	7	17	9	8	12	8
Grades 3-4	0	0	<1	0	0	0	0
<b>Triglycerides</b>							
All Grades	23	38	49	34	55	68	5
Grades 3-4	0	1	6	2	4	11	6
<b>Glucose</b>							
All Grades	15	11	15	14	16	25	20
Grades 3-4	<1	0	1	<1	0	2	2
<b>White Blood Cells</b>							
All Grades	19	35	11	14	13	10	14
Grades 3-4	3	6	3	4	2	<1	0
<b>Platelets</b>							
All Grades	<1	4	3	1	4	8	4
Grades 3-4	0	1	2	<1	0	2	0

Most Grade 3-4 laboratory abnormalities occurred with similar frequency when GW908 was administered alone or with ritonavir. Co-administration of twice daily ritonavir led to moderate increases in triglyceride levels and mild increases in cholesterol levels; an expected finding.

The frequency of laboratory abnormalities in the GW908 1400mg twice daily arm of study APV30001 was similar to those observed in patients treated with Agenerase alone. The laboratory profile for the GW908/ritonavir arms was similar to that of Agenerase/ritonavir, with the exception of notable increases in hepatic transaminase levels and triglycerides (see below). Also, except for more triglyceride increases in the twice daily arm, there were no differences in the frequency or severity of laboratory abnormalities between GW908/ritonavir once and twice daily.

#### C.6. Adverse Events of Special Interest

Metabolic abnormalities, including abnormalities of liver function, elevated triglycerides, cholesterol, and glucose, insulin problems, fat redistribution syndrome (central fat gain and/or peripheral fat loss, buffalo hump and changes in waist/hip ratios), are frequent in patients

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receiving PI-based therapy, and represent some of the major chronic adverse effects that limit successful adherence to antiretroviral therapy.

Abacavir-related hypersensitivity reactions (ABC HSR) have previously been reported to occur in approximately 9-10% of ABC recipients, with rare cases being fatal. The ABC labeling carries significant warnings advising clinicians and patients about the signs and symptoms of ABC HSR. The study protocols contained detailed sign, symptom, management and classification information for investigators. In addition the applicant used a central safety monitoring group to review any case suggestive of ABC HSR.

The chemical structure of amprenavir contains a sulfonamide-like moiety. Rash has been reported in Agenerase recipients with sulfonamide allergies in Phase 3 studies. It was hypothesized that patients treated with GW908 may experience similar outcomes since it is rapidly and almost completely metabolized to amprenavir.

Bleeding in hemophiliacs and hemolytic anemia have previously been reported in patients receiving amprenavir as Agenerase®. The GW908 database was reviewed to see if similar events were reported with this alternative formulation for delivering amprenavir. No patient who entered the pivotal studies had a history of hemophilia; thus it is unknown if, once GW908 enters general practice, if bleeding in this population will occur. It is reasonable therefore to include a similar Warning in the GW908 label as appears in the Agenerase label. Regarding hemolytic anemia, no cases were identified. In the Agenerase studies, the majority of patients were receiving zidovudine which is known to cause hemolytic anemia. It is again possible that once GW908 is more widely used, some patients will also receive zidovudine. The Warning related to hemolytic anemia in the Agenerase label will also be included in the GW908 label.

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, it was prudent to review the outcomes of any pregnancies to determine if the preclinical findings were a harbinger for poor clinical outcomes.

- **Fat-Redistribution Syndrome (Lipodystrophy)**

Patients who receive long-term PI and NRTI-based therapies are at risk for changes in body habitus due to fat redistribution (facial, arm, leg, buttocks, and trunk wasting, abdominal girth, breast enlargement, fat lump on back of neck, and lipomatosis).

In treatment naïve patients treated with GW908, increased abdominal girth, buffalo hump, and breast enlargement were the most common fat redistribution symptoms reported. Overall <1% of patients who received GW908 reported "lipodystrophy" as an adverse event. However, there were more patients who received GW908/ritonavir that experienced fat redistribution compared to those who received GW908 alone (5 vs. 2).

In the treatment experienced patients in study APV30003 baseline fat redistribution was expected to be present in some because of previous PI therapy and, in general, longer duration of HIV infection. Clinical symptoms of lipodystrophy were present at baseline in 43/106 (41%),

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46/106 (43%), and 44/103 (43%) of GW908/ritonavir once daily, GW908/ritonavir twice daily, and LPV/r patients, respectively. Lipodystrophy was assessed as increased in 11/43 (26%) of GW908/ritonavir once daily, 9/46 (20%) of GW908/ritonavir twice daily, and 9/103 (20%) of LPV/r recipients at week 48. In patients who did not have lipodystrophy at baseline, 10%, 15% and 7%, of patients in the GW908/ritonavir once daily, GW908/ritonavir twice daily, and LPV/r arms, respectively, reported lipodystrophy at week 48.

**Comment: In treatment naïve patients, co-administration of GW908 with ritonavir appeared associated with an increased frequency of lipodystrophy. In treatment experienced patients, new onset of fat redistribution occurred more often in patients treated with GW908/ritonavir.**

- **Triglyceride Levels**

Elevated triglycerides are known to be related to therapy with PIs, ritonavir in particular. In the pivotal studies, hypertriglyceridemia was reported in 23% of patients who received GW908 without ritonavir. When ritonavir was added, the frequency increased substantially (see Table 16).

In treatment naïve patients, most patients entered the studies with NCEP Lipid Category normal (<150 mg/dL) triglyceride levels. Among patients who received GW908 alone (study APV30001), 18% (27/148) shifted to the high (200-<500 mg/dL) or very high (>500 mg/dL) categories. With co-administration of ritonavir (study APV30002) the proportion of patients with shifts to the high or very high categories significantly increased, 46% (107/232). By comparison, approximately 36% (114/317) patients who received NFV had similar shifts.

In treatment experienced patients, most patients entered the study with normal (<150 mg/dL) or borderline high (150-<200 mg/dL) triglycerides. The median triglyceride change from baseline was highest among patients in the LPV/r arm followed by GW908/ritonavir twice daily and GW908/ritonavir once daily arms: +23 mg/dL, +12.4 mg/dL, and +7.5 mg/dL, respectively. Approximately 50% of patients in all three treatment arms experienced a shift to a high triglyceride value (200-<500 mg/dL) by the end of the study.

Overall, the frequency of Grade 3-4 elevations of triglycerides (>1200 mg/dL) was higher among patients who received GW908/ritonavir twice daily compared to GW908 alone or GW908/ritonavir once daily, and higher than the frequency observed in LPV/r recipients (see Table 17).

No adverse events directly related to high triglycerides reported were identified in the pivotal studies. Generally, this pattern was similar to that reported in clinical trials of patients treated with Agenerase®/ritonavir.

**Comment: Patients treated with GW908 with ritonavir are at higher risk for hypertriglyceridemia. All patients should undergo triglyceride monitoring during treatment and have elevated levels treated accordingly.**

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- **Cholesterol Levels**

Long-term exposure to PIs has been associated with increases in cholesterol levels and concerns about the possibility of increased cardiovascular morbidity and mortality.

A similar proportion of treatment-naïve patients who received GW908 or GW908/ritonavir reported hypercholesterolemia as adverse event (2%). However, more patients who received GW908/ritonavir experienced increases in total cholesterol levels compared to those who received GW908 alone, 17% versus 7%. Also, more patients who received GW908/ritonavir initiated anti-cholesterol therapy. In study APV30001 where GW908 was administered alone, 3% (5/166) initiated anti-cholesterol therapy compared to 5% (16/322) of patients who received GW908/ritonavir (study AVP30002). None of the patients in APV30001 who initiated anti-cholesterol therapy reported a cardiovascular adverse event. As described above, one patient who initially received GW908/ritonavir in study APV30002 died of a myocardial infarction with high cholesterol levels while still receiving GW908/ritonavir in a long-term roll over study.

The frequency of patients initiating anti-cholesterol therapy in the NFV arms of both studies was 3%.

Among PI-experienced patients, the majority entered the study with normal to borderline high total cholesterol levels. The median increase in total cholesterol levels was +10.6 mg/dL in the GW908/ritonavir once daily arm, +13.2 mg/dL in the twice daily arm, and +5.4 mg/dL in the LPV/r arm. Patients in the GW908/ritonavir twice daily arm had smaller HDL increases, +2.7 mg/dL compared to +5.0 mg/dL in the other two arms. Absolute LDLs were reduced in the GW908/ritonavir twice daily and LPV/r arms compared to the GW908/ritonavir once daily arm, -1.9 mg/dL, -1.9 mg/dL, and +1.2 mg/dL, respectively. However, more patients in the GW908/ritonavir twice daily arm had LDL values shift to the high (160-<190 mg/dL) or very high ( $\geq 190$  mg/dL) category, 21% versus 17% in the LPV/r arm.

Very few patients initiated anti-cholesterol therapy. One patient in the GW908/ritonavir once daily arm, three patients in the twice daily arm, and one patient in the LPV/r initiated anti-cholesterol agents. There were no clinical adverse events specifically related to increased cholesterol levels in any treatment arm.

**Comment: Addition of ritonavir led to increased frequency and severity of cholesterol levels. In treatment naïve patients, the data suggest that prolonged exposure to GW908/ritonavir may lead to sustained increases in cholesterol levels requiring pharmacologic intervention that could result in the emergence of cholesterol-related adverse events. Patients who initiate therapy with GW908 alone and with ritonavir should undergo cholesterol monitoring and receive anti-cholesterol therapy as warranted.**

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- **Glucose Levels**

Hyperglycemia has been reported as a metabolic complication of PI-based therapies. In general there were small median increases in glucose values in all treatment groups, and significant (Grade 3-4) elevations of glucose were rarely observed.

In study APV30003, 3% of GW908/ritonavir once daily, 5% of GW908/ritonavir twice daily and 4% of LPV/r patients had a history of diabetes mellitus at baseline. All parameters related to glucose metabolism, including fasting glucose, insulin levels, fasting insulin, and leptin were increased in the two Lexiva/ritonavir arms, while in the LPV/r arm all parameters decreased. Specifically, patients in the LPV/r arm had lower median change from baseline at week 48 compared to those who received GW908/ritonavir once or twice daily, -1.8 mg/dL versus +1.8 and +7.2 mg/dL. The difference in median change between GW908/ritonavir twice daily and LPV/r reached statistical significance,  $p=0.0003$ ). In both GW908/ritonavir arms, there were increases in median insulin levels compared to the LPV/r arm, +5.0 and +10.8 pmol/L versus -7.2 pmol/L. There were no cases of treatment emergent diabetes mellitus reported in study APV30003.

Among treatment naïve patients, treatment emergent glucose abnormalities were rare. In study APV30001, one patient in the GW908 arm who entered the study with a history of diabetes mellitus experienced a Grade 3 glucose elevation. A patient in the NFV arm with a family history of diabetes experienced a Grade 4 glucose elevation. One patient in the GW908/ritonavir group in study APV30002, with a family history of type 2 diabetes entered with a normal glucose value, and developed type 2 diabetes. This patient had Grade 3 glucose elevations on two occasions.

- **Abacavir Hypersensitivity Reaction**

Abacavir hypersensitivity reaction (ABC HSR) has been reported to occur in approximately 9-10% of patients who receive ABC, and in rare cases it is fatal. ABC HSR is characterized by the appearance of symptoms including fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), lethargy or malaise, and sometimes respiratory symptoms (dyspnea, sore throat, cough), musculoskeletal symptoms (myalgia, myolysis, arthralgia), headache, paraesthesia and edema. The reaction can occur at any time during treatment with ABC, but usually occurs within the first six weeks of initiation of treatment (median time to onset is 11 days).

In studies APV30001 and APV30002, all patients received ABC as a component of their antiretroviral regimen. In these two studies, the frequency of ABC HSR was 9%, and was similar in frequency and severity between the GW908 and NFV arms.

In study APV30003, 116 patients used ABC as a component of their optimized background regimen. Five cases of ABC HSR occurred (4.3% overall frequency), two in the GW908/ritonavir once daily, one in the GW908/ritonavir twice daily, and two in the LPV/r arm.

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Most were Grade 2 or 3 in severity, with some Grade 4. Typically ABC was discontinued and/or replaced with another NRTI, and most cases resolved upon discontinuation of ABC.

One death possibly related to ABC HSR was reported. The patient was a male in the NFV arm of study APV30001 who three days after initiating study treatment developed severe depression and a mild rash. The following day (Day 4) the subject returned to the clinic with nausea, vomiting, fever, headache and dehydration, but no rash. On Day 5 he was hospitalized with a diagnosis of sepsis, severe dehydration, and fever. Blood cultures, chest X-ray and a computer tomography scan of the brain were negative. On the day of admission, he had a seizure and developed renal failure. Six days after admission he aspirated and expired the next day. The cause of death was reported as aspiration pneumonia and sepsis. In the investigator's opinion, the dehydration and fever were possibly related to the use of study drugs but the fatal aspiration pneumonia and sepsis were not related. The applicant's Global Clinical Safety and Pharmacovigilance (GCSP) group reviewed this case and determined that this case met an ABC HSR case definition.

Six patients discontinued study APV30002 due to ABC HSR, three each from each treatment arm.

**Comment: The frequency and severity of ABC HSR were generally consistent with previously reported data.**

- **Hepatotoxicity**

Most patients in the three pivotal studies had normal or mildly elevated baseline ALT and AST levels. The majority of shifts in these parameters were of one grade (e.g., Grade 1 to 2). A small proportion of patients experienced Grade 3 or 4 elevations, primarily among patients who entered the studies co-infected with hepatitis B or C. Overall, most patients had normalization of hepatic transaminase levels by the end of the studies. It did not appear that the addition of ritonavir significantly increased either the frequency or severity of ALT or AST increases.

Approximately 22% of patients who received GW908 had a baseline history of co-infection with chronic hepatitis B or C, or both. Overall, more patients with hepatitis co-infection developed Grade 3-4 ALT and AST elevations compared to non-co-infected patients. Almost twice as many patients with hepatitis C had a severe or Grade 3-4 adverse event (primarily elevated AST or ALT levels) compared to those without hepatitis C, 35% and 19%, respectively. A similar pattern was observed among patients co-infected with hepatitis B.

Additional patients in IND and non-IND studies experienced significant hepatic transaminitis, all of whom were co-infected with a hepatitis virus.

Total bilirubin elevations were reported rarely among patients treated with GW908, 1% (2/166) of patients. There was a slight increase in bilirubin levels when GW908 was co-administered with ritonavir (13/534, 2%). The majority of bilirubin elevations were Grade 1 or 2 in severity.

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**Comment: All patients who receive GW908 alone or with ritonavir should be monitored closely for hepatotoxicity during treatment. Patients co-infected with hepatitis B and/or C appear to be at a higher risk for drug induced hepatotoxicity. This precautionary information will be included in the labeling.**

- **Sulfonamide Reactions**

A total of 57/700 (8%) of GW908 recipients were known to have a preexisting sulfonamide allergy, 11 of whom (19%) reported rash. The median onset and duration were 11 and 13 days, respectively. One patient with a pre-existing sulfonamide allergy experienced Stevens-Johnson Syndrome. This patient started co-trimoxazole prior to entry and continued while on study. On day 10 he experienced signs and symptoms consistent with ABC HSR; ABC was replaced with zidovudine. On day 24 he experienced nausea, vomiting and diarrhea after taking his co-trimoxazole. Subsequently he was admitted to hospital and experienced peeling of his lips. He was treated with steroids and the events resolved approximately two weeks after onset. Thus, it was not clear if his Stevens-Johnson Syndrome was due to his underlying sulfonamide allergy, exposure to ABC, or both.

Among patients with no history of sulfonamide allergy, 17 patients (92/538) experienced rash. There were no differences between patients who received GW908 and GW908/ritonavir. Across the comparator arms, 19/513 (9%) patients entered studies with a known sulfonamide allergy. Of these, 40% (19/47) reported rash.

**Comment: Overall, more patients without a history of sulfonamide allergy reported rash. Although the numbers of patients with sulfonamide allergy were small, the frequency and severity of rash in patients treated with GW908 was similar to that reported with Agenerase. Therefore, caution should be exercised when GW908 is to be administered to a patient with a known sulfonamide allergy.**

- **Pregnancies**

Female patients of childbearing potential were required to have evidence of a negative pregnancy test prior to entry, and had to agree to use a proven barrier method of contraception. A total of eight females became pregnant while receiving GW908.

In study APV30001, one female in the GW908 1400 BID arm became pregnant approximately 20 weeks after starting study medications. Her antiretrovirals were discontinued and she gave birth to a healthy male infant.

In study APV 30002, five pregnancies were reported among women receiving GW908 1400 mg plus ritonavir 200 mg once daily. Once pregnancy was diagnosed, in all but one case antiretroviral therapy was discontinued. Pregnancy outcomes included: spontaneous abortion (1), elective termination (1), and delivery of normal healthy infants (3).

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In study APV30005 (long term open label access protocol), two pregnancies were reported; outcomes data are not available. For the first, the woman became pregnant approximately 24 weeks after starting GW908 700 mg plus ritonavir 100 twice daily and her antiretrovirals were discontinued. The second woman had been receiving GW908 1400 twice daily for approximately five months; once pregnancy was discovered her antiretrovirals were discontinued.

No pregnancies were reported in study APV30003.

**Comment: Pre-clinical data suggested that GW908 might have a negative impact on pregnancy. This concern did not appear to be borne out in the clinical database, but the number of pregnancies was very low. Because no adequate and well controlled studies have been conducted, based on the pre-clinical data, GW908 will be classified as Pregnancy Category C.**

#### **D. Adequacy of Safety Testing**

Preclinical and early clinical testing assisted in identifying adverse clinical and laboratory events likely attributable to GW908. Data from over 2000 persons exposed to GW908 with and without ritonavir demonstrated that preclinical data appeared to predict the observed clinical and laboratory adverse events. There were no significant safety differences based on gender or race.

#### **E. Summary of Critical Safety Findings and Limitations of Data**

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 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.

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, with an increase in frequency with co-administration of ritonavir. The frequency and severity were within expected parameters; thus, it does not appear that patients treated with GW908 are at either less or more risk of these events compared to other PIs.

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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. One patient with a pre-existing sulfonamide allergy experienced Stevens-Johnson Syndrome.

### VIII. Dosing, Regimen, and Administration Issues

Recommended doses of Lexiva™ for treatment naïve patients are 1400 mg twice daily, 1400 mg once daily co-administered with 200 mg of ritonavir, or 700 mg plus ritonavir 100 mg twice daily. Although not formally studied, the GW908/ritonavir twice daily dose for naïve patients is supported by pharmacokinetic data and safety data from treatment-experienced patients. Co-administration with ritonavir will lead to increased frequency of vomiting and diarrhea, and metabolic abnormalities, such as hypertriglyceridemia, hypercholesterolemia, and hepatic transaminitis. The trade off between a potentially more convenient dosing regimen and increased risk of adverse events will need to be carefully balanced as clinicians consider using GW908 as a component of an initial antiretroviral regimen.

For treatment experienced patients, the recommended dose is GW908 700 mg plus 100 mg of ritonavir administered twice daily. Once daily dosing is not recommended for this patient population.

Based on the above review, it was not possible to determine if individual Tablet Variants had any impact on safety or efficacy.

Lexiva™ may be administered without regard to food intake.

No dosage adjustments are required for patients with renal insufficiency

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, for treatment naïve patients, is 700mg twice daily without ritonavir.

There are no data on use of amprenavir with ritonavir, as either GW908 or Agenerase®, in treatment-experienced patients with any degree of hepatic impairment, and there are no data on use of GW908 alone in 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 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.

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### IX. Use in Special Populations

Overall, there was no evidence of treatment or safety effects of either GW908 or GW908/ritonavir among racial, gender, or age categories.

#### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The applicant conducted analyses to determine if there was a treatment effect by gender. Across the two naïve studies APV30001 and APV30002, the applicant concluded that both sexes had a good antiviral response that was similar to the overall rate observed in the whole population. The FDA review found that in general, female patients tended to respond less well compared to males, 52% versus 66%. Similar differences were observed in the control arms. These differences were not sufficient to warrant specific dosing recommendations for one or the other sex.

In study APV30003, the majority of patients were male (181/212). Male subjects responded similarly in the GW908/ritonavir once and twice daily arms, but their responses were generally lower than in the LPV/r arm. There were insufficient female patients upon which to reach a conclusion about differences compared to males.

#### B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

##### Age

Due to the paucity of patients 13-18 and >65 years of age, no meaningful conclusions about treatment effect or safety by age could be drawn. Although the numbers of elderly patients with HIV-1 infection is overall relatively small, there do not appear from preclinical or clinical studies any specific contraindications to using GW908 in this age group. Also, despite elderly patients often having decreased renal function; no dosage adjustment is necessary in patients with renal insufficiency (see **Pharmacokinetics and Pharmacodynamics**).

##### Race

The applicant concluded that race did not influence treatment outcomes. The findings demonstrate that Caucasian patients responded somewhat better than other ethnicities. But the differences did not reach the level of statistical significance.

#### C. Evaluation of \_\_\_\_\_

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#### D. Comments on Data Available or Needed in Other Populations

As described above, 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 treatment experienced patients. In addition, there are no data on patients with more severe hepatic disease (Child-Pugh score 9 to 15), and because of the single strength of Lexiva™ Tablets, no dosing recommendations could be made.

#### X. Conclusions and Recommendations

##### A. Conclusions

###### 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. Specifically, when administered twice daily without ritonavir, the proportions of patients with HIV-1 RNA <400 c/mL and <50 c/mL were 64% and 54%. The corresponding values for Lexiva administered once daily with ritonavir were 69% and 58%, respectively. This clinical benefit was sustained through at least 48 weeks that was generally comparable to a regimen containing Viracept® (nelfinavir, NFV, Agouron Pharmaceuticals), which is generally used as a first-line protease inhibitor. The data demonstrate no efficacy penalty for administration of GW908 once daily with ritonavir and represents an option when a once daily regimen is being considered.

In PI-experienced patients, GW908/ritonavir administered twice daily produced lower reductions from baseline in HIV-1 RNA (the applicant's primary endpoint), 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 an established comparator agent, Kaletra® (lopinavir/ritonavir, LPV/r, Abbott Laboratories).

###### Risks

GW908 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.

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

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antiviral responses and delay the emergence of resistance. This hypothesis is based on a finding that no amprenavir resistance-associated mutation emerged in 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 accepted by clinicians and patients and the increased risks are considered expected and manageable.

In PI-experienced patients, once daily administration of GW908/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 908 and 908/ritonavir. Thus, GW908 represents an additional option for patients who might benefit from a protease inhibitor-based antiretroviral regimen. The applicant submitted a robust safety and efficacy database to support approval of GW908 for treatment of treatment-naïve and PI-experienced HIV-1 infected patients.

#### **B. Recommendations**

Based on review of the materials submitted in this NDA, from a clinical perspective the application for use of Lexiva™ Tablets in combination with other antiretroviral agents for treatment of HIV-1 in adults is recommended for approval.

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