CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20828

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF THE NEW DRUG APPLICATION
NDA 20-828

DRAFT

Date Received: 12 May 1997
Date Assigned: 19 May 1997
Date Completed: 05 November 1997

Drug: Saquinavir

Trade name: FORTOVASE™

Chemical name: Cis-N-tert-Butyl-decahydro-2-(2(R)-hydroxy-4-phenyl-
                       3(S)-((N-(2-quinolylcarbonyl)-L-asparaginyl)amino)butyl)-
                       (4aS,8aS)-isoquinoline-3(S)-carboxyamide

Formulation: Soft gelatin capsule containing 200 mg amorphous
                       saquinavir free base dissolved in a glyceride excipient

Dosage: 1200 mg p.o., TID

Proposed indication: FORTOVASE™ is indicated for use in combination with
                       other antiretroviral agents for the treatment of HIV
                       infection. This indication is based on a clinical study that
                       showed a reduction in both mortality and AIDS-defining
                       clinical events for patients who received INVIRASE® in
                       combination with HIVID® compared to patients who
                       receive either INVIRASE® or HIVID® alone. This indication
                       is also based on studies that showed increased saquinavir
                       concentrations and improved antiviral activity for
                       FORTOVASE™ 1200 mg TID compared to INVIRASE® 600
                       mg TID.

Sponsor: Hoffmann-La Roche, Inc.
                       340 Kingsland Street
                       Nutley, NJ 07110-1199

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1. RESUME

Hoffmann-La Roche, Inc. submitted this NDA to seek FDA approval for saquinavir soft gelatin capsule (SQV-SGC), a protease inhibitor to be used in combination with other antiretroviral agents in the treatment of HIV infection. SQV-SGC is an improved formulation of the currently marketed saquinavir hard gelatin capsule (SQV-HGC) developed to achieve higher bioavailability of the drug. SQV-SGC at the recommended dosage, 1200 mg p.o. TID, has been shown to be safe and well tolerated in more than 500 patients for a duration of at least 48 weeks. The drug has also been proven to have antiretroviral activity in reducing HIV RNA levels and improving CD4 cell counts. Together with the clinical benefits previously demonstrated in studies with SQV-HGC in reducing mortality and AIDS-defining clinical events, SQV-SGC is hereby recommended for traditional approval to be used as indicated.

2. MATERIAL REVIEWED

This NDA consisted of 113 volumes. This review was based on the following volumes:

- Volume 1.2, 1.3:   Labeling, application summary
- Volume 1.52 - 1.113:   Clinical and statistical data (studies NV15107, NV15182)
- Volume 2.   Clinical and statistical data (studies NV15107, NV15182)
- Volume 3.1- 3.3:   Clinical and statistical data (study NV15355)
- Volume 10.15 - 10.25: Clinical and statistical data (study NV15355)

In addition, the reviewers also examined 56 additional submissions during the review period.

3. CHEMISTRY, MANUFACTURING AND CONTROL

Saquinavir (SQV), an HIV protease inhibitor.

SQV is currently marketed in a hard gelatin capsule (HGC) formulation. However,

SQV-HGC has poor oral bioavailability of 4%. The soft gelatin capsule (SGC) formulation was developed to provide higher exposure to SQV and thereby enhancing the therapeutic benefit to patients.

Reviewer's Comment

For a comprehensive review of the chemistry, manufacturing and control, please see the chemistry review by Dr. Paul Liu.

4. PHARMACOLOGY AND TOXICOLOGY

4.1. Animal Toxicology Studies

The sponsor had previously conducted comprehensive animal toxicity and toxicokinetic studies of saquinavir mesylate, the active drug moiety in the SQV-HGC formulation. These studies showed that the drug was well tolerated at high plasma exposure with no reproductive, teratogenic, or developmental effects. Mutagenicity and genotoxicity assays were negative. The excipient has a generally-recognized-as-safe (GRAS) status. The following additional animal toxicology studies to evaluate the safety of SQV-SGC formulation were conducted.

4.1.1. Oral Studies in Rats

A seven-day exploratory toxicity conducted in Dawley rats orally administered with SQV-SGC in   up to 1400 mg/kg/day for 7 days did not increase plasma exposure (AUC_{0-8h}) or plasma concentrations (C_{max}) relative to that produced by saquinavir mesylate.   did not appear to have local adverse effects in

the rat gastrointestinal tract. No further studies were conducted in rats.

4.1.2. Oral Studies in Dogs

Marmosets were found to be intolerant to large amounts of the   · lipoidal excipient. Therefore, safety studies in non-rodent species were alternatively performed in beagle dogs which proved to be a predictive model for adverse events seen in clinical studies with SQV-SGC. These studies identified adverse effects in the gastrointestinal system and confirmed the hepatotoxicity of SQV-SGC.

In 13-week dog studies, a dose-related increase in emesis, soft stools, and diarrhea was observed at doses at or above 100 mg/kg/day administered once a day. These gastrointestinal toxicities were reduced by dividing the daily dose. There were no gross or histopathologic changes observed in the GI tracts.   .   appeared to contribute to the adverse GI effects and caused slight reductions in food consumption and body weight.

Saquinavir produced hepatotoxicity in dogs exposed to high doses of 300-700 mg/kg/day as evidenced by increased levels of alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltransferase (GGT) and alkaline phosphatase (AP). According to the sponsor, most of these cases were not accompanied by histologic changes. However, one dog given 700 mg/kg/day had mild histopathologic changes in the liver (not otherwise specified by the sponsor) after four weeks. This dog also had elevated ALT, AST, GGT, AP, bilirubin, cholesterol and triglycerides.

The no-observable-adverse-effect-level (NOAEL) for hepatotoxicity in dogs was 270 mg/kg/day which gave a mean plasma exposure (AUC_{24}) of 86 μg.h/mL. This AUC_{24} is approximately 4-fold higher than that seen in human studies of SQV-SGC 1200 mg TID (20 μg.h/mL).

        given up to 34 g/day (the daily quantity of   excipient in 1200 mg tid regimen of SQV-SGC is 14 g) did not alter lipid metabolism in dogs. Serum triglycerides, free fatty acids and cholesterol were apparently unaffected.

4.2. Toxicity in Combination with Ritonavir

Ritonavir (RTV) is a potent inhibitor of cytochrome P_{450} CYP3A4 isoenzyme which is responsible for the clearance of SQV. Coadministration of these drugs results in substantial increase of SQV concentrations. In a pharmacokinetic study with healthy volunteers, plasma concentrations of SQV were increased 17 to 22-fold in

the presence of RTV. SQV did not exert significant effect on the pharmacokinetics of RTV. There was no apparent increase of adverse gastrointestinal effects seen with combination treatment compared to single drug treatments.

4.3. Teratology and Reproductive Toxicity Studies

The sponsor had previously conducted comprehensive studies for saquinavir mesylate (NDA 20-628). Rabbits and rats in these studies were maximally exposed (AUC_{0-24h}) to approximately 10 μg.h/mL of saquinavir mesylate which did not provide a safety margin for the new SQV-SGC formulation, since a therapeutic dosage of 1200 mg tid can produce approximately 20 μg.h/mL. Nevertheless, the sponsor did not plan further studies citing the relative low teratogenic risk of SQV due to minimal placental transfer. Reproductive toxicity studies with SQV-SGC were limited to embryotoxicity and teratogenicity study in Dawley rats. No adverse effects on embryo-fetal growth and development were observed in rats given 500 mg/kg/day of degraded and non-degraded SQV-SGC on days 6-17 of gestation.

4.4. Mutagenicity, Genotoxicity, and Carcinogenicity Studies

Since data have been available for saquinavir mesylate, the sponsor only conducted limited mutagenicity study (Ames test) and genotoxicity study (human chromosome aberration assay) using degraded SQV-SGC formulation and   alone with or without metabolic activation. These studies revealed no mutagenic activity, clastogenic or aneuploidogenic effects.

Carcinogenicity studies with saquinavir mesylate in rats and mice are currently ongoing at doses giving AUC_{0-24h} of 10 μg.h/mL and 24 μg.h/mL, respectively. As SQV-SGC confers AUC_{0-24h} of approximately 20 μg.h/mL in patients, no safety margin exists relative to the carcinogenicity study in rats. However, citing the lack of genotoxicity, the sponsor has no plan to conduct carcinogenicity study with the new formulation.

Reviewer's Comment

Please see the pharmacology/toxicology review by Dr. K.M. Wu for further details.

5. MICROBIOLOGY

The specific inhibitory activity against HIV proteinase (both HIV-1 and HIV-2) of SQV has been established in vitro and in vivo. The following section will provide an overview of studies conducted to explore the effects of increased SQV exposure to

genotypic and phenotypic changes that can result in altered SQV sensitivity.

5.1. Genotypic Analysis

Study NV15107 was an open-label, dose-ranging study for SQV-SGC (n =88; CD4 100-500 cells/mL; HIV RNA > 20,000 copies/mL). Viral genomes recovered from 22/32 patients receiving the 1200 mg TID dosage for a median of 32 weeks of treatment showed characteristic G48V and L90M mutations and G48V/L90M double mutation previously seen in studies with the HGC formulation. From the results of study EV14757, a SQV-HGC high-dose study. it was apparent that higher exposure to SQV resulted in decreased incidence of these mutations. The 3600 mg/day group had 40% incidence of either G48V or L90M mutation; whereas the incidence in the 7200 mg/day (which gave approximately half the plasma exposure of SQV-SGC 1200 mg TID regimen) was 10%. The double mutation was absent in both groups. Combination therapy with ddC appeared to reduce the emergence incidence of G48V and L90M mutations.

5.2. Phenotypic Analysis

Although there is a high level of natural genetic variation in "wild-type" HIV, G48V and L90M mutations are absent in the untreated HIV-infected population. It appeared that these mutations were selected during SQV therapy. However, preliminary data to date on phenotypic profile from the two studies mentioned above were insufficient to definitively support a change in SQV sensitivity. Data from other trials (NV14256, NV14255, O13328), nevertheless, suggested a modest (< 10-fold) reduction in SQV sensitivity in a small number (6/13) of isolates bearing L90M mutation. Only one isolate with double 48V/90M mutation had greater than 20-fold change. The sponsor therefore concluded that G48V and L90M should be viewed as genetic markers for potential SQV resistance.

Reviewer's Comment

Please see the microbiology review by Dr. Nara Battula for further details.

6. CLINICAL BACKGROUND

6.1. Related INDs and NDAs

6.2. Foreign Experience

SQV-SGC formulation has not been approved in any foreign country. One of the studies involving SQV-HGC formulation submitted in this NDA (study NV14256) was conducted in multiple centers in the U.S. and Canada.

6.3. Human Pharmacology, Pharmacokinetics and Pharmacodynamics

6.3.1. Pharmacokinetics

The pharmacokinetic properties of SQV are not affected by gender, age, or weight; however, there is a high degree of inter- and intrasubject variability. Pharmacokinetic studies with SQV-HGC formulation showed wide tissue distribution (10 L/Kg), and high plasma clearance (50-100 L/h). In the plasma, SQV was more than 97% protein bound. The mean residence time of SQV following IV administration was approximately 7 hours. At steady state the plasma concentrations of SQV increased in a non-linear, dose-dependent, greater-than-proportional manner after both single and multiple dosing.
In vitro studies showed that more than 90% of SQV underwent rapid hepatic microsomal metabolism, mediated predominantly by CYP3A4 isoenzyme of cytochrome P_{450}, into a number of mono- and dihydroxylated inactive compounds. Approximately 96% of SQV was eliminated in feces, and less than 4% excreted in urine.

Following multiple dosing (600 mg TID) in HIV-infected patients, the mean 8-hour area under the plasma concentration curve (AUC_8) of SQV-HGC was 866 ng.h/mL. This was approximately twice that observed in healthy volunteers receiving the same regimen.

The absolute bioavailability of SQV-HGC was low (approximately 4%). This was thought to be due to low intestinal absorption, P-glycoprotein-mediated luminal secretion, and considerably high first-pass metabolism. The absorption of SQV-HGC was substantially enhanced (approximately 18-fold) by food with high fat contents.

The new SQV-SGC formulation showed an approximate 3-fold increase of bioavailability (estimated by AUC_{0-12h}). Following multiple dosing of SQV-SGC 1200 mg TID in HIV-infected patients (study NV15107), the mean AUC_8 was 7249 ng.h/mL. This represented an approximately 8-fold increase of drug exposure compared to that of SQV-HGC 600 mg TID regimen. The drug plasma concentrations in HIV-infected patients were double those seen in volunteers. It

was postulated that the increased levels were due to higher absorption and reduced metabolism in the former group. The SQV-SGC formulation produced an approximate 7-fold increase in bioavailability when administered within 10 minutes of a standard meal compared to the fasted state.

Reviewer's Comments

1. The sponsor recently submitted preliminary data from a pharmacokinetic drug interaction substudy conducted on a number of patients (n = 21) from study NV15182 who had been on relatively long-term treatment with SQV-SGC. The data unexpectedly revealed that plasma concentrations of SQV were substantially lower than the previously determined steady-state levels. The mean AUC_8 of SQV in these patients (measured between weeks 36 to 51 of treatment) was 2103 ng.h/mL compare to the steady-state level of 7249 ng.h/mL measured at week 3. Repeat analysis performed in a different cohort of patients (n = 11) showed a mean AUC_8 of 3485 ng.h/mL in plasma samples obtained between weeks 61 and 69. At the time of this NDA review, no definitive explanations for this observation have been substantiated. Whether the lower AUC affects virological or immunological responses in these patients is still not clear when this review is written.

2. Please see the biopharmaceutic review by Dr. Prabhu Rajagopalan for further details.

6.3.2. Drug Interactions

6.3.2.1. Drug Interaction Studies with SQV-HGC

The extensive CYP3A4-mediated first-pass metabolism of SQV resulted in a number of drug-drug interactions with compounds metabolized by this enzyme. Drug interaction studies conducted with the SQV-HGC formulation showed that coadministration with inhibitors of CYP3A4 (e.g., ketoconazole, ranitidine, grape fruit juice) increased exposure of SQV up to 2.5-fold. Ritonavir, a potent CYP3A4 inhibitor, increased the bioavailability of SQV up to 20-fold in healthy subjects. Likewise, delavirdine increased plasma concentration of SQV by 5-fold. Coadministration with inducers of CYP3A4 (e.g., phenobarbital, phenytoin, dexamethasone, carbamazepine) resulted in reduction of SQV exposure. Rifampicin and rifabutin substantially decreased SQV concentration by 80% and 40%, respectively.

6.3.2.2. Drug Interaction Studies with SQV-SGC

Concurrent administration of SQV-SGC and clarithromycin in healthy volunteers resulted in increased SQV exposure by approximately 2.8 fold, and clarithromycin by 1.5 fold. The elimination half-life of SQV was not prolonged.

SQV-SGC, when coadministered with terfenadine, produced an approximately 2-fold accumulation of unmetabolized terfenadine. While an increase of unmetabolized terfenadine has been shown to prolong the QTc interval leading to cardiac arrhythmia, this study did not identify a clinically significant treatment effect on the QTc.

Interaction studies with SQV-SGC and other protease inhibitors have been conducted. Coadministration of SQV-SGC with indinavir and nelfinavir resulted in 3.6 and 3.9-fold increase of SQV plasma concentrations, respectively.

Reviewer's Comment

The sponsor had planned on conducting the pharmacokinetic drug interaction studies between SQV-SGC and ketoconazole, rifabutin and rifampin on patients from study NV15182. However, due to the lower-than-expected SQV plasma concentrations encountered during the analysis (see Reviewer's Comment, section 6.3.1), these studies have not been completed at the time of this NDA review. These studies will be conducted as phase 4 commitments (see section 12).

6.3.3. Special Populations

The sponsor reported that results of study NV15107 did not show a correlation between SQV-SGC plasma concentration and biochemical markers of renal function in HIV-infected patients with normal or mild renal impairment. Similar observation was noted with the HGC formulation. However, no study has been conducted on patients with severe renal dysfunction.

Patients with normal or mild hepatic dysfunction did not have increased exposure to SQV, SGC or HGC formulation. However, long-term exposure to SQV resulted in mild elevation (grade 1) of AST and ALT. There are no available data on the effect of severe hepatic impairment on the pharmacokinetics of SQV-SGC.

6.4. Other Relevant Background Information

Per previous agreement with DAVDP/FDA in a pre-NDA meeting, the sponsor submitted this NDA 20-828 for traditional rather than accelerated approval. The traditional approval was based on the traditional approval of SQV-HGC. The clinical benefit of SQV-HGC has been established by study NV14256, which was previously submitted for review under NDA 20-628 (SQV-HGC).

7. BRIEF DESCRIPTIONS OF CLINICAL TRIALS

A brief summary of all clinical trials submitted in this NDA is presented in this section. These studies will be reviewed in detail in section 9.

7.1. Core Studies

To support this NDA, the sponsor submitted data from three open-label studies with the SQV-SGC formulation, NV15107, NV15182, and NV15355 conducted under IND 41099. NV15107 was a dose-ranging study. NV15182 was a safety study in 442 patients. NV 15355 was an ongoing comparative study between SQV-HGC and SQV-SGC formulations.

7.1.1. Protocol NV15107 (Dose-Range Study)

This was an ongoing, multicenter, randomized, open-label, parallel group study to determine the safety, pharmacokinetics and activity of SQV monotherapy with a range of doses as outlined in Table 7.1.1. The primary monotherapy treatment period was 8 weeks in length to select the optimal dose of SQV-SGC. In the extension phase of the study, patients were allowed to switch to the optimal SQV-SGC dose as monotherapy or in combination with additional antiretroviral therapy.

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Table 7.1.1. Overview of Protocol NV15107

Patient Population	Treatment*	n	Sex M/F	Age (years)
- CD4: 100 - 500 cells/mm³ - HIV RNA > 20,000 copies/mL - Naive to protease inhibitor treatment	- SQV-HGC 600 mg TID	11	11/0	31 - 45
	- SQV-SGC 400 mg TID	12	10/2	23 - 46
	- SQV-SGC 800 mg TID	33	30/3	27 - 68
	- SQV-SGC 1200 mg TID	32	30/2	30 - 59

* After 8 weeks, patients were allowed to add other antiretroviral therapy.
(Source: NV15107)

7.1.2. Protocol NV15182 (Safety Study)

This was an ongoing, multicenter, open-label study to determine primarily the safety of SQV-SGC 1200 mg TID in combination with other antiretroviral agents. To rapidly enroll patients for this study, the CD4 cell count, HIV RNA level, and concomitant antiretroviral use (excluding other protease inhibitors) were not specified in the inclusion/exclusion criteria. Primary safety and efficacy descriptive analyses were to be performed at week 24, and follow-up analyses at week 48. The study is summarized in Table 7.1.2.

Table 7.1.2. Overview of Protocol NV15182

Patient Population	Treatment	n	Sex M/F	Age (years)
- Unspecified HIV RNA level and CD4 cell count - At least 75% naive to protease inhibitors	- SQV-SGC 1200 mg TID + 2 RTIs of choice	442	398/44	15 - 71

(Source: NV15182)

7.1.3. Protocol NV15355

This is an ongoing randomized, open-label, parallel comparative arm, multicenter study to evaluate the antiviral activity and safety of SQV-HGC and SQV-SGC formulations in combination with two nucleoside antiretroviral drugs in treatment naive HIV-infected patients. The comparative phase of the study was to last 16 weeks. Subsequently patients were to be allowed to switch to the treatment arm

of choice for a total duration of 48 weeks. Primary safety and activity analyses were to be done at week 16 and follow-up analyses at week 48. The study is summarized in Table 7.1.3.

Reviewer's Comment

Per agreement between DAVDP and the sponsor, the 16-week safety and efficacy data from this study would be submitted for review in this NDA.

Table 7.1.3. Overview of Protocol NV15355

Patient Population	Treatment	n	Sex M/F	Age (years)
- CD4: unspecified - HIV RNA ≥ 5000 copies/mL - Naive to protease inhibitors - <4 weeks of nucleoside treatment	- SQV-HGC 600 mg TID + 2 RTIs of choice	81	74/7	18 - 63
	- SQV-SGC 1200 mg TID + 2 RTIs of choice	90	83/7	18 -60

(Source: NV15355)

7.2. Supportive Studies

7.2.1. Protocol NV14256 (Clinical Endpoint Study)

This completed study was a randomized, double-blind, parallel group study to determine the safety and clinical benefit of SQV-HGC in advanced HIV-infected patients. In this 80-week study, time to first AIDS-defining event or death was the primary clinical endpoint, and time-to-death was secondary. The CD4 cell count and HIV RNA level were utilized as efficacy surrogate markers. The study was designed to investigate the value of HIV RNA and CD4 cell count as surrogate endpoints in advanced HIV disease. The study summary is presented in Table 7.2.1.

Table 7.2.1. Overview of Protocol NV14256

Patient Population	Treatment	n	Sex M/F	Age (years)
- 50 < CD4 ≤ 300 cells/mm³ - ZDV intolerance or - discontinued ZDV use	- ddC 0.75 mg TID	325	294/31	20 - 74
	- SQV-HGC 600 mg TID	327	298/29	22 - 69
	- SQV-HGC 600 mg TID + ddC 0.75 mg TID	318	301/17	22 - 70

(Source: NV14256)

7.2.2. Protocol EV14757 (High-Dose Study)

This completed open-label, dose-escalating study was designed to investigate the safety, tolerability, pharmacokinetics, and activity of high-dose regimens of SQV-HGC, 3600 mg/day and 7200 mg/day given q4h for 24 weeks. Patients who tolerated the treatment with sustained surrogate marker response were given the option of 120 weeks of extended monotherapy with the current SQV regiment alone or in combination with AZT or ddC, or to receive SQV-HGC 600 mg TID. The study outline is presented in Table 7.2.2.

Table 7.2.2. Overview of Protocol EV14757

Patient Population	Treatment	n	Sex M/F	Age (years)
- CD4: 200-500 cells/mm³	- SQV-HGC 600 mg q4h	20	19/1	24 - 54
	- SQV-HGC 1200 mg q4h	21	21/0	26 - 50

(Source: NV14757)

8. CLINICAL TRIALS

8.1. Protocol NV15107

8.1.1. Protocol Title

A randomized, parallel, open-label study comparing saquinavir hard gelatin formulation (600 mg TID) to saquinavir soft gelatin formulation [(400 mg, 800 mg, 1200 mg) TID] for 8 weeks in HIV-infected patients.

8.1.2. Objectives

The objectives of this study were:

A.   To compare the antiviral activity, safety and pharmacokinetics in HIV-
     infected patients of saquinavir hard gelatin formulation (SQV-HGC), 600 mg
     TID to saquinavir soft gelatin formulation (SQV-SGC) (400mg TID, 800mg
     TID, or 1200 mg TID) administered for an eight week period

B.   To determine an optimal dose for SQV-SGC.

8.1.3. Study Design

This was a randomized, open-label, multi center, parallel four-arm phase I/II fixed
dose study in HIV-infected patients with CD4 cell counts between 100 and 500
and plasma HIV-RNA > $2x10^4$ copies/mL.

Eighty-eight HIV-positive patients were to be stratified by previous history of
antiretroviral use (naive, less than 8 weeks, or greater than 8 weeks) and
randomized to one of the four treatment regimens:

A.	SQV-HGC 600 mg TID	$(n_1 = 11)$
B.	SQV-SGC 400 mg TID	$(n_2 = 11)$
C.	SQV-SGC 800 mg TID	$(n_3 = 33)$
D.	SQV-SGC 1200 mg TID	$(n_4 = 33)$

> *Comment: A total of 88 patients were randomized into the study. The
> sponsor does not make reference to a total number of patients screened for
> this study. Of the 88 patients randomized, 84 subjects completed the initial
> 8 week treatment period. All 88 patients were evaluated for safety,
> pharmacokinetics and efficacy (intent to treat analysis).*

This clinical trial consisted of up to two treatment phases; a primary phase of 8
weeks, and an extension phase to last 96 weeks. In the primary treatment phase,
patients were given SQV monotherapy, either standard dose of the SQV-HGC
formulation or one of several doses of the SQV-SGC formulation. After 8 weeks,
patients were permitted to add other antiretroviral therapy, of their choice in the
extension phase. Subsequent to the identification of the most active SQV-SGC
dose, patients were given the option of switching to the most active dose as
monotherapy or in combination with other antiretroviral therapy.

Comment: The efficacy results from this study will focus primarily on the 8 week treatment period. The option of adding antiretroviral therapy and/or switching to the optimal dose of SQV-SGC complicates the interpretation of - the antiviral activity results beyond 8 weeks.

SQV-HGC and SQV-SGC were to be administered every 8 hours, within 2 hours after a meal or substantial snack. In addition, a standard breakfast was to be consumed within 30 minutes and to be finished within 10 minutes before taking the morning dose on the pharmacokinetic sampling days.

Comment: It has been well established that the bioavailability of saquinavir can be enhanced in the presence of a high fat content meal.

Patients were followed for signs and symptoms, and chemistry and hematology assessments at weeks 1-4, 8, 24, then every 8 weeks thereafter. Plasma HIV-RNA samples were obtained at weeks 1,2,3,4 and 8 whereas, T cell subsets were obtained at weeks 4 and 8. After week 8, T cell subsets and plasma HIV-RNA levels were obtained four times during a calendar year at the investigator's discretion.

Samples from all patients were to be obtained for intensive pharmacokinetic assessments on days 7 to 14, and days 21 to 28.

Rationale for Study Design

Based on data from a small trial (EV14757) sponsored by an academic investigator, higher doses of SQV-HGC (3600 mg and 7200 mg per day) resulted in greater increases in CD4 cell counts and plasma HIV RNA than standard doses. However, the sponsor felt that it was not feasible to administer higher doses of this formulation due to the number of capsules (36) needed to deliver 7200 mg a day. SQV-HGC formulation has been limited by poor bioavailability (4%). Therefore, the sponsor has developed a new formulation (SQV-SGC) which increases SQV concentrations by approximately three fold over the currently marketed SQV-HGC.

In study 15107, marketed dose of SQV-HGC 600 mg TID was chosen as the comparator to three doses of SQV-SGC. The SQV-SGC 400 mg TID dose was chosen because it was predicted to achieve similar concentrations to the SQV-HGC 600 mg TID. SQV-SGC 1200 mg TID was predicted to produce concentrations similar to the SQV-HGC 7200 mg/day regimen as seen in study EV14757. The SQV-SGC 800 mg TID dose was included to ensure an adequate description of the dose-concentration and exposure-concentration curves.

In this study the sponsor was attempting to determine a regimen of the SQV-SGC formulation that would produce superior increases in CD4 cell counts and superior decreases in plasma HIV RNA compared to the currently marketed SQV-HGC 600 mg TID regimen. It is also important to note that although SQV-SGC has improved bioavailability over the currently marketed formulation, the approved SQV-HGC dose was also doubled in the 1200 mg TID cohort.

For ethical considerations patients only remained on saquinavir monotherapy for 8 weeks and then were given the option of adding additional antiretroviral agents and/or switching to the most active dose of SQV-SGC.

8.1.4. Patient Population

8.1.4.1. Inclusion Criteria

The eligibility criteria included male and female HIV-infected patients who were protease inhibitor naive, 18 years or older, with CD4 ≥100-500 cells/mm3, HIV RNA > 20,000 copies/mL, no history of transfusion dependency, hemoglobin ≥8 g/dL, absolute neutrophil count (ANC) > 750 cells/mm^3, platelet count ≥50,000/mm^3, transaminases < 2.5X upper normal limit, total bilirubin < 1.5X upper normal limit, and adequate contraception practice.

> *Comment: In this small study, inclusion of patients with and without prior antiretroviral experience complicate interpretation of study results.*

8.1.4.2. Exclusion Criteria

Patients with malabsorption, inability to maintain adequate oral intake, grade 3/4 laboratory or clinical abnormalities, active opportunistic infection or serious AIDS-defining events, unexplained persistent fever (≥38.5°C, ≥14 days), chronic diarrhea (≥3 loose stools/day, ≥14 days), malignancy and history of non-Hodgkin's lymphoma were to be excluded. Pregnancy, breast-feeding, inadequate contraception were also reasons for exclusion.

> *Comment: Exclusion of patients with CD4 cell counts < 100 cells/mm3 may make study results difficult to generalize for this subgroup. Specifically, patients with advanced HIV infection may experience malabsorption syndromes that could result in different pharmacokinetic, safety and efficacy profiles than that of the population enrolled.*

8.1.5. Concomitant Medication

Patients were to have no prior protease inhibitor experience. Patients were to be stratified on the basis of prior antiretroviral experience. For those patients who were presently receiving antiretroviral therapy a 28 day wash out period was mandated prior to study entry. Concomitant antiretrovirals were not allowed during the initial 8-week treatment period.

Concomitant treatment with nephrotoxic, hepatotoxic, cytotoxic, and bone marrow toxic drugs were to be closely monitored. Medications whose hepatic metabolism could potentially be inhibited by SQV (e.g., clindamycin, dapsone, pyrazinamide, ergotamine, terfenadine, clarithromycin, nifedipine, and other dihydropyridine class calcium channel blockers) were to be prescribed with caution. Ketoconazole, itraconazole, fluconazole, miconazole, erythromycin, cimetidine and ranitidine which could potentially increase SQV plasma concentration were prohibited during the first 8 weeks of the study and were to be used with caution afterwards. Rifampin and rifabutin could decrease SQV concentrations and thus were not allowed in the first 8 weeks of the study and were to be used with caution afterwards. Phenytoin and carbamazepine could similarly induce hepatic metabolism of SQV and were to be avoided. In addition coadminstration with grapefruit juice, ganciclovir and foscarnet were prohibited and use of nevirapine was discouraged.

8.1.6. Treatment Compliance

Compliance was assessed by drug dispensing and return records and counting of unused capsules in the medicine container for patients at each visit.

> *Comment: The sponsor did not provide information on treatment compliance.*

8.1.7. Endpoints

8.1.7.1. Primary Endpoints

The primary endpoints of this study were changes in absolute CD4 cell counts and plasma HIV RNA. These endpoints were evaluated at the end of the initial primary 8-week treatment period and at 24-weeks for the extension phase.

8.1.7.2 Secondary Endpoints

Secondary endpoints included pharmacokinetic parameters such as C_{max}, t_{max}, t_{lag}, AUC_8.

> *Comment: Please see Dr. Prabhu Rajagopalan's review for the results of pharmacokinetic analysis.*

8.1.7.3. Safety Endpoints

Investigators classified each adverse event and abnormal laboratory value as mild, moderate, severe, or potentially life-threatening, corresponding to ACTG protocol grades 1 to 4, respectively.

8.2.8. Premature Discontinuation of Treatment

Patients could voluntarily withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study due to adverse events, intercurrent illness, treatment failure, protocol violation, laboratory toxicity, or any other administrative reasons.

8.1.9. Analytical and Statistical Plans

8.1.9.1. Efficacy

All efficacy assessments were based on the intent-to-treat population which was defined as all randomized patients with at least one pre-treatment and one post-baseline efficacy measurement. A patient with no baseline or post-baseline value was excluded from the analysis of that parameter only.

Changes in CD4 and plasma HIV RNA over time were analyzed using AUC and AUCMB as defined below.

- AUC: area under the curve of absolute values up to visit t divided by t (t = actual study day).

- $AUCMB_t$:   AUC minus baseline

- NAUC: AUC divided by baseline

- $NAUCMB_t$:   NAUC divided by baseline

The quantitative plasma HIV RNA level was performed using the Amplicor HIV-1 Monitor™ test. The sponsor used 400 copies/mL as the lower limit of assay quantification.

No specific methodology for CD4 cell count was specified.

Due to the exploratory nature of this study and the small sample size, the sponsor did not plan any formal statistical tests.

8.1.9.2. Safety

Patients were evaluated for safety if they had received at least one dose of trial medication and had at least one follow-up safety assessment.

The adverse events were to be graded by the investigator as:

- Mild: resolved or easily tolerated on therapy

- Moderate: sufficiently uncomfortable to interfere with usual activity

- Severe: incapacitating the ability to perform normal daily activity and potentially life-threatening.

- Serious: presenting a threat to the patient's well being; i.e., fatal, life-threatening, permanently disabling, requiring hospitalization, causing congenital abnormality or malignancy, or overdose.

Each adverse event was to be evaluated for the relationship to the test drug (unrelated, remote, possible, probable) based on temporal relationship, patient's clinical status, known pattern of test drug, and reappearance of adverse event upon rechallenge.

Laboratory parameters (hematology, clinical chemistry and baseline urinalysis) were evaluated for abnormalities using the ACTG grading criteria. Shift in the ACTG grade from baseline were tabulated by treatment group and parameter. Shifts from grade 0 (normal) to grade 3 or 4 during treatment, or shift from grade 1 to grade 4 would be classified as "marked" laboratory abnormality.

8.1.10. Results

8.1.10.1. Patient Disposition

8.1.10.1.1. Eight-Week Treatment Period

A total of 88 subjects were enrolled. Table 8.1.10.1.1.A summarizes the sponsor's assessment of the number of patients evaluable for safety, efficacy (intent-to-treat population) and pharmacokinetic assessments during the 8-week treatment period.

Table 8.1.10.1.1.A. Summary of Patient Disposition (8 weeks)

	Number of Patients Evaluated			Reasons for Permanent Discontinuation		
Dosing Regimen	Safety	Efficacy	Pharmaco kinetics	Adverse events	Other reasons	Deaths
SQV-HGC 600 mg TID	11	11	11	0	1	0
SQV-SGC 400 mg TID	12	12	12	0	0	0
SQV-SGC 800 mg TID	33	33	33	1	0	0
SQV-SGC 1200 mg TID	32	32	32	0	2	0

Source: NV15107

The sponsor states that all 88 patients were evaluated for safety, pharmacokinetics and for the intent to treat analysis of efficacy for the 8 week treatment period.

Table 8.1.10.1.1.B. summarizes FDA's assessment of patients who discontinued study drug and the reasons for discontinuation for each of the four arms during the 8 week treatment period. A total of three patients discontinued therapy; one in the SQV-HGC 600 mg TID arm, one in the SQV-SGC 800 mg TID arm and two in the SGC 1200mg TID arm. There were no deaths during the 8 week treatment period.

Table 8.1.10.1.1.B. Reasons for Premature Discontinuation of Therapy (8 weeks)

Reason	SQV-HGC 600mg N=11	SQV-SGC 400mg N=12	SQV-SGC 800mg N=33	SQV-SGC 1200mg N=32	Total N=88
Myopathy	0	0	1	0	1
Nausea, Dyspepsia, Gastric Distress	0	0	1	1	2
Refused Treatment/Non-Cooperative/Withdrew Consent	1	0	0	0	1
Skin Rash	0	0	0	1	1
Total	1	0	1*	2	4*

*Patient 75 experienced both GI symptoms and myopathy
Source: FDA's analysis of NV15107

Comment: The sponsor and investigators stated that patient 0022 and patient 0160 discontinued from study due to "other reasons". However, patient 22 required a dose reduction after 15 days of SQV-SGC 1200 mg TID therapy due to gastric distress which was unresolved at the time the patient withdrew consent. Therefore, Table 8.1.3.1.1.B includes patient 0022 as a patient who discontinued therapy due to an adverse event. Likewise, patient 0160 developed a rash while on SQV 1200 mg TID and the rash had not resolved at the time the patient withdrew consent. Thus, patient 0160 was reclassified as discontinuating therapy due to adverse event.

8.1.10.1.2. Twenty-Four Week Extension Period

Of the 88 patients who entered the study, 74 patients completed 24 weeks of treatment. Table 8.1.10.1.2.A shows the sponsor's assessment of patient disposition through the 24 week extension period.

Table 8.1.10.1.2.A. Summary of Patient Disposition (24 Weeks)

Dosing Regimen	Number of Patients Evaluated		Reason for Permanent Discontinuation		
	Safety	Efficacy	Adverse events	Other reasons	Deaths
SQV-HGC 600 mg TID	11	11	0	2	0
SQV-SGC 400 mg TID	12	12	1	1	0
SQV-SGC 600 mg TID	33	33	1	4	0
SQV-SGC 1200 mg TID	32	32	0	5	0

Source: NV15107

Table 8.1.10.1.2.B summarizes FDA's assessment of patients who discontinued and the reasons for discontinuation for the four arms of the study during the 24 week extension period. A total of fourteen patients discontinued therapy; four of which discontinued therapy prior to week 8. There were no deaths during this extension phase.

Table 8.1.10.1.2.B. Reasons for Premature Discontinuation of Therapy (24 weeks)

Reason	SQV-HGC 600mg N = 11	SQV-SGC 400mg N = 12	SQV-SGC 800mg N = 33	SQV-SGC 1200mg N = 32	Total N = 88
Adverse Event	0	1	3	4	8
Refused Treatment/Non-Cooperative/Withdrew Consent	2	1	1	0	5
Insufficient Therapeutic Response			1	1	2
Total	2	2	5	5	14

Source: FDA's analysis of NV15107

Patients were allowed to add new antiretroviral therapy after the initial eight week treatment period. Most patients started additional antiretroviral medication after week 8. In addition, patients were given the option to switch to SQV-SGC 1200 mg TID, which appeared to be the most active treatment regimen. However, due to the delays in implemeting a switch in SQV regimen, most patients switched to SQV-SGC 1200 mg after week 13.

Table 8.1.10.1.2.C describes the number of patients who started a new antiretroviral treatment and/or switched to the 1200 mg saquinavir SQV-SGC dose.

TABLE 8.1.10.1.2.C. Summary of Patients with Treatment Changes (New Antiretroviral Treatment and/or Switching to SQV-SGC 1200 mg dosage)

Subgroup I:	SQV-HGC 600 mg N=11	SQV-SGC 400 mg N=12	SQV-SGC 800 mg N=33	SQV-SGC 1200 mg N=32
New antiretroviral treatment after week 8	6 (54.5%)	12 (100%)	26 (78.8%)	28 (87.5%)
No new antiretroviral treatment after week 8	5 (45.4%)	0 (0%)	7 (21.2%)	4 (12.5%)
Subgroup II:				
Switch to 1200 mg SQV-SGC	8 (72.7%)	9 (75.0%)	28 (84.9%)	N/A
Switch to 1200 mg SQV-SGC	3 (27.3%)	3 (25.0%)	5 (15.2%)	N/A

Source: NV15107 (Vol. 66: p. 18; Table 3)

The most commonly used antiretroviral therapies were lamivudine and zidovudine which were used by approximately twice as many patients as any other antiretrovirals.

8.1.10.1.3. Forty-Eight Week Safety Update:

The sponsor states that at the time of the 48 week safety analysis, 40 patients had withdrawn from study participation.

Table 8.1.10.1.3 displays the sponsor's assessment of reasons for premature treatment withdrawals.

Table 8.1.3.1.3. Reasons for Premature Discontinuation of Therapy (48 Weeks)

Reason	SQV-HGC 600 mg N = 11	SQV-SGC 400 mg N = 12	SQV-SGC 800 mg N = 33	SQV-SGC 1200 mg N = 32
Insufficient therapeutic response	2 (18.3%)	0	7 (21.2%)	6 (18.8%)
Refused treatment/non-cooperative/withdrew consent	3 (27.3%)	2 (16.7%)	5 (15.2%)	5 (15.6%)
Adverse event	1 (9.1%)	1 (8.3%)	3 (9.1%)	1 (3.1%)
Lost to follow-up	0	0	1 (3.0%)	1 (3.1%)
Change of residency	0	0	1 (3.1%)	0
Miscellaneous	0	0	0	1 (3.1%)
Total of patients with premature withdrawal	6 (54.5%)	3 (25%)	17 (51.5%)	14 (43.8%)

Source: NV15107 (48-Week Safety Update)

Comment: There did not appear to be a substantial difference among treatment regimens in the percentage of treatment withdrawals due to adverse events.

8.1.10.2. Protocol Deviations

During the study, one patient had a protocol violation. Patient 0160 initiated additional antiretroviral treatment prior to week 8.

8.1.10.3. Demographic Data

Table 8.1.10.3.A shows the demographic data and the baseline HIV RNA levels and CD4 cell counts of the study population.

Table 8.1.10.3.A. Summary of Demographic Data

Treatment	SQV-HGC 600 mg N = 11	SQV-SGC 400 mg N = 12	SQV-SGC 800mg N = 33	SQV-SGC 1200 mg N = 32	Total N = 88
SEX					
Male	11 (100%)	10 (83%)	30 (91%)	30 (94%)	81 (92%)
Female	0 (0%)	2 (17%)	3 (9%)	2 (6%)	7 (8%)
AGE (years)					
Mean	39.2	35.4	38.2	41.8	38.6
Range	31 - 45	23 - 46	27 - 68	30 - 59	23 - 68
RACE					
White	9 (82%)	11 (92%)	31 (94%)	27 (84%)	78 (89%)
Black	1 (9%)	0 (0%)	0 (0%)	2 (6%)	3 (3%)
Oriental	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (1%)
Hispanic	1 (9%)	1 (8%)	1 (3%)	3 (9%)	6 (7%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Baseline plasma HIV RNA (Log$_{10}$ copies/mL)					
Mean	5.08	4.77	5.18	5.09	5.03
Standard deviation	0.44	0.38	0.42	0.49	0.43
Baseline CD4 cell counts (cells/mm^3)					
Mean	248	195	228	210.4	220.3
Standard deviation	108.5	60.5	113.9	87.5	92.6

Source: NV15107 (Vol. 62: Tables 3 and 6)

8.1.10.4. Efficacy Outcomes

8.1.10.4.1. Eight-Week Treatment Period

The sponsor stated that no statistical tests were planned due to the exploratory character of the study. The sponsor descriptively summarized changes from baseline for HIV-RNA and CD4 cell counts. In addition, the sponsor conducted subgroup analyses to determine the effect of previous antiretroviral treatment on changes in HIV-RNA levels and CD4 cell counts.

The sponsor concluded that SQV-SGC 1200 mg was the optimal dose for further exploration based on the results shown in Table 8.1.10.4.1.A. Plasma HIV RNA results are displayed as the median changes (interquartile range) and AUCMB for all SQV-SGC treatment regimens during the 8-week treatment period.

Table 8.1.10.4.1.A. Summary of HIV RNA Change from Baseline (log_{10} copies/mL)

Treatment Group	SQV-HGC 600 mg	SQV-SGC 400mg	SQV-SGC 800mg	SQV-SGC 1200mg
Median change	-0.25	-0.19	-0.42	-0.64
Interquartile range	-0.43 to -0.08	-0.85 to 0.07	-0.90 to -0.09	-1.76 to -0.16
Median AUCMB change	N/A	-0.27	N/A	-0.82
Interquartile AUCMB range		-0.53 to -0.00		-1.41 to -0.45

N/A: Data not given
Source: NV15107

The sponsor stated that decreases in plasma HIV RNA were dose related and that the greatest effect was observed with the 1200 mg cohort. It was also stated that the treatment effect of 600 mg SQV-HGC was slightly better than the 400 mg SQV-SGC group. The plasma HIV RNA nadir was achieved between weeks 2.5 and 4.

Table 8.1.10.4.1.B shows the median change (interquartile range) and AUCMB for CD4 Cell Counts for all treatment regimens during the 8 week treatment period.

Table 8.1.10.4.1.B. Summary of CD4 Cell Count Change from Baseline (cells/mm^3)

Treatment Group	SQV-HGC 600mg	SQV-SGC 400mg	SQV-SGC 800mg	SQV-SGC 1200mg
Median change	32.5	35.5	68.8	58.3
Median AUCMB change	32.7	20.3	54.2	57.2
Interquartile AUCMB range	-9.2 to 65.0	-16.2 to 67.6	28.8 to 76.9	17.9 to 92.8

Source: NV15107

8.1.10.4.2. Twenty-Four Week Extension Period

The sponsor descriptively summarized changes from baseline for HIV-RNA and CD4 cell counts. In addition, the sponsor conducted subgroup analysis for the effect of previous antiretroviral treatment on changes in plasma HIV-RNA levels and CD4 cell counts. Summarized below in Table 8.1.10.4.2 are the median (interquartile range) change of HIV RNA from baseline for all treatment groups at week 16. The sponsor concluded that a further reduction in plasma HIV RNA was achieved beyond week 8 when patients either switched to 1200 mg SQV-SGC and/or received additional antiretroviral therapy.

Table 8.1.10.4.2. Summary of HIV RNA Change from Baseline (log$_{10}$ copies/mL)

Treatment Group	SQV-HGC 600mg	SQV-SGC 400mg	SQV-SGC 800mg	SQV-SGC 1200mg
Median change	-0.85	-0.68	-1.05	-1.17
Interquartile range	-1.75 to -0.25	-1.19 to -0.10	-2.38 to -0.44	-2.88 to -0.42

Source: NV15107

The sponsor noted that these results were maintained up to week 24 in all SQV-SGC groups. The sponsor attributes the differences in HIV-RNA changes at weeks 16 and 24 between the four treatment groups to the fact that not all patients had been switched to the 1200 mg SQV-SGC dose. Twenty three of the twenty six patients who received 1200 mg SQV-SGC had a reduction in plasma HIV RNA

below baseline at either week 16 or 24.

The sponsor noted that there was no clear separation with regard to CD4 cell counts between doses. The largest effect seen during the 24 week extension phase was in the 600 mg SQV-HGC group after new antiretroviral treatment was added and/or switched to 1200 mg SQV-SGC. The median change from baseline for the 600 mg SQV-HGC group was 135 cells/mm^3. Twenty four of the twenty eight patients who received 1200 mg SQV-SGC had an increase in CD4 cell counts compared to baseline.

8.1.10.4.3. Subgroup Analysis of HIV-RNA and CD4 Cell Counts

The sponsor states that patients who had less than 8 weeks of prior antiretroviral treatment had numerically larger decreases in plasma HIV RNA than those patients who received antiretroviral treatment for greater than 8 weeks prior to study enrollment. The median change from baseline at week 8 for the 1200 mg SQV-SGC group was -1.21 $\log_{10}$ copies/mL for patients with less than 8 weeks of prior treatment and -0.56 $\log_{10}$ copies/mL for patients with more than 8 weeks of prior antiretroviral treatment. However, there did not apear to be a difference between naive and non naive patients with respect to decreases in HIV RNA levels. The median change from baseline to week 8 was -0.68 $\log_{10}$ copies/mL for naive patients and -0.57 $\log_{10}$ copies/mL for non-naive patients.

Similar to the plasma HIV RNA subgroup results, patients who had less than 8 weeks of prior antiretroviral therapy tended to have larger increases in CD4 cell counts than those with more than 8 weeks of prior antiretroviral treatment. Similar effects were seen in the subgroup analysis of naive and non-naive patients. The median change from baseline in CD4 cell counts was 96.0 cells/mm^3 (33.0 to 159.0) for patients with less than 8 weeks prior antiretroviral treatment and 54.5 (38.0 to 102.5) for patients with more than 8 weeks of prior antiretroviral treatment.

8.1.10.5. Safety Outcomes

All 88 patients are included in the analysis of safety. Patients were exposed to different dosage levels and different lengths of treatment. The data is analyzed taking into consideration the length of exposure and total amount of saquinavir received. Data from patients who discontinued drug due to adverse events were reviewed in an attempt to identify possible risk factors associated with ADEs. All serious ADEs were reviewed individually in an effort to recognize possible risk factors associated with the ADEs. There were no deaths in this study.

8.1.10.5.1. Drug Exposure

The extent of saquinavir exposure is described in Table 8.1.5.1.A. This table includes data from baseline up to week 48. It is important to note that this table does not reflect time on the original randomized treatment because the majority of patients switched to SQV-SGC 1200 mg. According to the sponsor, there were 78 patients who received SQV-SGC 1200 mg for part or all of the study. Table 8.1.5.1.B describes the extent of exposure to SQV-SGC 1200 mg. The 46 patients who switched to SQV-SGC 1200 mg had a median treatment period on 1200 mg SQV-SGC of 29-32.5 weeks. The 32 patients who were originally randomized to SQV-SGC 1200 mg had a median treatment period of 52 weeks (range 2-70 weeks)

TABLE 8.1.5.1.A. EXTENT OF SAQUINAVIR EXPOSURE

Treatment duration (weeks)	SQV-HGC 600 mg N = 11	SQV-SGC 400 mg N = 12	SQV-SGC 800 mg N = 33	SQV-SGC 1200 mg N = 32
0 to 2	11	12	33	32
3 to 4	10	12	32	31
5 to 12	10	12	32	31
16 to 18	10	11	32	30
24	9	10	28	27
36	7	10	24	24
48	6	9	21	23

Source: NV15107

8.1.10.5.2. Adverse Events

8.1.10.5.2.1. Overview of Adverse Events

The sponsor reported that 82 of the 88 patients reported at least one adverse event during the 24 week study period. In addition, 85 of the 88 patients reported at least one adverse event during the 48 week study period. The most common adverse event observed in this clinical trial were gastrointestinal complaints such as abdominal discomfort, diarrhea, dyspepsia and nausea. There was no evidence of

new gastrointestinal events emerging between weeks 24 and 48.

The sponsor presented adverse event data based on the investigator's assessment of severity and causality. Determining causality of adverse events is difficult; therefore, in review of this study adverse events will be summarized by treatment group regardless of perceived causality with the drug. Separate tables of adverse events are summarized by treatment group excluding those events perceived as unrelated to study drug.

Table 8.1.10.5.2.1.A summarizes adverse events reported by at least 3 patients (any intensity) during the 8 week treatment period. Table 8.1.10.5.2.1.B summarizes adverse events reported for the SQV-SGC 1200 mg cohort at weeks 8, 24 and 48 . It is important to note that between weeks 8 and 24, patients were given the option of adding additional antiretroviral therapy and/or switching to SQV-SGC 1200 mg. Therefore, dose comparisons are difficult to assess for the entire 48 week extension period. Table 8.1.10.5.2.1.C summarize the number of patients experiencing adverse event by severity excluding those unrelated to study drug through week 8. Table 8.1.10.5.2.1.D summarizes the number of patients who were originally randomized to receive SQV-SGC 1200 mg and experienced an adverse event of any severity at weeks 8, 24 and 48. Adverse event data are presented according to the patients' original randomized treatment arm; therefore, tables do not provide dose comparisons through weeks 24 and 48. These treatment periods may be a more accurate assessment of long term safety data for those patients who switched to SQV-SGC 1200 mg in combination with new antiretroviral therapy.

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Table 8.1.10.5.2.1.A. Summary of Adverse Events for Eight-Week Treatment Period (Without Regard to Causality)

	SQV-HGC 600 mg (n = 11)	SQV-SGC 400mg (N = 12)	SQV-SGC 800 mg (N = 33)	SQV-SGC 1200 mg (N = 32)
All body systems				
Total number of patients with at least one adverse event	7 (63.6%)	10 (83.3%)	31 (93.9%)	26 (81.3%)
Total number of adverse events	24	31	120	98
Gastrointestinal				
Diarrhea	3 (27.3%)	0	8 (24.4%)	9 (28.1%)
Nausea	0	4 (33.3%)	6 (18.2%)	4 (12.5%)
Dyspepsia	0	0	5 (15.2%)	4 (12.5%)
Abd. discomfort/pain	0	0	6 (18.2%)	5 (15.6%)
Body as a whole				
Edema	0	0	0	3 (9.4%)
Fatigue	0	0	5 (15.2%)	
Headache	0	0	6 (18.2%)	3 (9.4%)
Fever	0	0	0	3 (9.4%)
Dermatological				
Rash/maculopapular rash/dermatitis/xeroderma	0	0	4	5 (15.6%)
Respiratory				
Sinusitis	0	0	5 (15.2%)	3 (9.4%)
Pharyngitis	0	0	3 (9.1%)	0
Musculo-skeletal				
Arthralgia	0	0	4 (12.1%)	0
Myalgia	0	0	3 (9.1%)	0

Source: NV15107 (Vol. 62: Appendix 22)

Table 8.1.10.5.2.1.B. Adverse Events for SQV-SGC 1200 mg Cohort at Weeks 8, 24 and 48 (Without Regard to Causality)

	Week 8	Week 24	Week 48
All body systems			
Total number of patients with at least one adverse event	26 (81.3%)	29 (90.6%)	30 (93.8%)
Total number of adverse events	98	185	248
Gastrointestinal			
Diarrhea	9 (28.1%)	16 (50.0%)	18 (56.3%)
Nausea	4 (12.5%)	8 (25.0%)	10 (31.3%)
Dyspepsia	4 (12.5%)	7 (21.9%)	10 (31.3%)
Abd. discomfort/pain	5 (15.6%)	10 (31.2%)	13 (40.1%)
Flatulence	0	4 (12.5%)	6 (18.8%)
Body as a whole			
Asthenia	0	3 (9.4%)	3 (9.4%)
Edema	3 (9.4%)	3 (9.4%)	4 (12.5%)
Fatigue	0	4 (12.5%)	7 (21.9%)
Headache	3 (9.4%)	6 (18.8%)	7 (21.9%)
Fever	3 (9.4%)	3 (9.4%)	4 (12.5%)
Dermatological			
Rash/maculopapular rash/dermatitis/xeroderma	5 (15.6%)	11 (34.4%)	13 (40.1%)
Sinusitis	3 (9.4%)	5 (15.6%)	6 (18.8%)
Cough	0	3 (9.4%)	4 (12.5%)
Pharyngitis	0	9 (28.1%)	9 (28.1%)
Musculoskeletal			
Arthralgia	0	0	4 (12.5%)
Pain Musculo-skeletal	0	4 (12.5%)	4 (12.5%)
Psychiatric Disorders			
Anxiety	0	5 (15.6%)	5 (15.6%)
Depression	0	6 (18.8%)	9 (28.1%)

Source: NV15107 (Vol. 62: Appendix 22; Vol. 67: Appendix 15; Safety Update, p.

119)

TABLE 8.1.10.5.2.1.C. Summary of Adverse Event[1] by Severity (8-Week Treatment Period)

Treatment	Mild	Moderate	Severe	Life-Threatening
SQV-HGC 600 mg	5	2	1	0
SQV-SGC 400 mg	6	3	0	0
SQV-SGC 800 mg	19	10	0	1
SQV-SGC 1200 mg	13	8	3	0

[1] Excluding adverse events unrelated to treatment
Source: FDA's analysis of NV15107

This table differs from the sponsor's assessment. The sponsor reported 17 mild adverse event for SQV-SGC 800 mg cohort, whereas an FDA assessment determined that there were 19 mild adverse events for the SQV-SGC 800 mg group. Additionally, the sponsor reported 7 moderate adverse events for 1200mg group, whereas an FDA assessment determeined that there were 8 moderate adverse events for this group.

TABLE 8.1.10.5.2.1.D. Summary of Adverse Event[1] by Severity for SQV-SGC 1200 mg Cohort (Weeks 8, 24 and 48)

Week	Mild	Moderate	Severe	Life-Threatening
8	13	8	3	0
24	20	15	6	0
48	20	16	6	0

[1] Excluding adverse events unrelated to treatment
Source: FDA's analysis of NV15107 (Vol. 62: Tables 12&13, Appendix 23)

This table differs from the sponsor's assessment. The sponsor reported 18 mild adverse event for SQV-SGC 1200 mg cohort at week 24, whereas an FDA

assessment determined that there were 20 mild adverse events for this group. Additionally, the sponsor reported 14 moderate adverse events for 1200mg group at week 24, whereas an FDA assessment determined that there were 15 moderate adverse events for this group. It can be concluded that no new adverse events were observed between weeks 24 and 48 for the SQV-SGC 1200 mg cohort and for patients who were originally randomized to the SQV-HGC formulation and SQV-SGC 400 mg and 800 mg. One additional mild adverse event was reported for a patient who was originally randomized to the SQV-HGC formulation cohort.

8.1.10.5.2.2. Serious and Life-threatening Adverse Events

Table 8.1.10.5.2.2 lists all patients having serious adverse events throughout the 48 week study period. A serious adverse event is an event that is life threatening, that results in severe or permanent disability, cancer, or a congenital anomaly, that requires or prolongs hospitalization, or that is due to a study drug overdose, regardless of relationship to saquinavir. The seriousness of an adverse event is independent of its severity.

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TABLE 8.1.10.5.2.2. PATIENTS EXPERIENCING SERIOUS ADVERSE EVENTS

Patient	Treatment	Treatment Period	Reason	Severity	Action taken
16327/0092	SQV-HGC 600mg	8	Pneumonia Cryptosporidiosis Lymphadenitis	Severe Moderate	Hospitalization Hospitalization Hospitalization
16249/0045	SQV-HGC 600mg	24	Diarrhea Abdominal Colic	Severe Severe	Hospitalization Hospitalization
16248/0010	SQV-SGC 400mg	24	Acidosis Metabolic	Severe	Hospitalization
16247/0143	SQV-SGC 400mg	48	Meningitis	Severe	Unknown
16248/0011	SQV-SGC 800mg	24	Gastritis	Severe	Hospitalization
16327/0095	SQV-SGC 800mg	24	Nausea Vomiting Diarrhea Suicide Attempt Drug Dependence	Moderate Moderate Moderate Severe Severe	Hospitalization Hospitalization Hospitalization Hospitalization Hospitalization
16338/0061	SQV-SGC 800mg	24	Diarrhea Headache Dehydration Nausea	Severe Severe Severe Moderate	Hospitalization Hospitalization Hospitalization Hospitalization
16247/0145	SQV-SGC 800mg	48	Hernia	Severe	Unknown
1628/003	SQV-SGC 1200mg	24	Hypertension	Mild	Unknown
16328/0151	SQV-SGC 1200mg	24	Drug Dependence Depression	Moderate Severe	Hospitalization Hospitalization
16337/0112	SQV-SGC 1200mg	24	Abdominal Pain Abdominal Discomfort	Severe Severe	Hospitalization Hospitalization
16337/0109	SQV-SGC 1200mg	48	Anxiety Depression Suicide Attempt	 Life-thng	Unknown

Source: NV15107 (Vol. 62: Sec. 3.4.4, Appendix 24; Vol. 66: Sec. 3.34, Appendix 16; 48-week Safety Update, Appendix 8)

A total of 26 serious adverse events were reported by 12 patients through week 48 of this study. Of the 26 serious adverse events, 16 were considered unrelated, 6 remotely related and 4 possibly related by investigators. It is important to note that patients were given the option of adding additional antiretroviral therapy to study medication after week 8.

Due to the May 1997, FDA Public Health Advisory Letter regarding reports of new onset of diabetes mellitus, hyperglycemia or exasserbation of pre existing diabetes mellitus in patients receiving protease inhibitor therapy, the following serious adverse event is of interest. This letter referenced five cases of diabetic ketoacidosis in patients who either were or were not reported to be diabetic at baseline.

> Patient 1640/0010: A 38 year old female, who randomized to receive SQV-SGC 400 mg, had a history of non-insulin dependent diabetes, and was admitted to the hospital on study day 188 with dehydration and ketoacidosis secondary to vomiting. The investigator considered metabolic acidosis to be severe in intensity and unrelated to study medication.

Since cases of diabetic ketoacidosis has been documented through the MedWatch program, the investigators assessment that this event is unrelated to saquinavir may not be correct.

8.1.10.5.2.3. Adverse Events Associated with Premature Discontinuation of Treatment

8.1.10.5.2.3.1. Serious Adverse Events

The sponsor did not attribute any premature treatment discontinuations due to serious adverse events. However, after reanalysis of the data it was concluded that patients 0112 and 0011 were discontinuations due to serious adverse events for the following reasons.

> Patient 0011 received SQV-SGC 800 mg from study days 1-96. This patient interrupted medication dosing on days 97-110 and then continued SQV-SGC 800 mg from day 111-134. On day 134 the sponsor lists this patient as early termination due to "refused treatment/non cooperation/withdrew consent." On day 72 the patient presented with diarrhea, arthralgia and headache which was considered to be of moderate severity and severe nausea. On day 114 the patient was diagnosed with severe gastritis (which

was considered a serious event by the investigator). All these events were unresolved at the time of study discontinuation. Therefore this reviewer considers patient 0011 to discontinue treatment due to a serious adverse event.

Patient 0112 received SQV-SGC 1200 mg from study days 1-14. The patient experienced numerous dose reductions through day 163. The patient developed severe abdominal pain and discomfort on day 111. These events were considered serious and did not resolve until day 199. The sponsor listed this patient as a premature termination due to "refused treatment/non cooperation/withdrew consent" on study day 163. Therefore, this reviewer considers patient 0112 to discontinue treatment due to a serious event because the event was not resolved at the time of termination.

8.1.10.5.2.3.2. Non-serious Adverse Events

The sponsor states that a total of six patients withdrew from the study due to adverse events, two during the first part of the study while on their original randomized treatment, and four between weeks 24 and 48. However in a FDA reassessment of the data it was noted that 20 patients withdrew from the study due to adverse events; 18 patients for non serious adverse events and 2 patients for serious adverse events. The majority of these patients had an ongoing or unresolved gastrointestinal adverse events such as diarrhea, nausea and dyspepsia, or fatigue at the time of discontinuation from study drug. Patients were considered to be "withdrawn" if an adverse event was ongoing or did not resolve at the time of drug discontinuation.

8.1.10.5.3. Deaths

There were no deaths reported during the 48 week study period.

8.1.10.5.4. Laboratory Findings

Table 8.1.10.5.4.A list the marked laboratory abnormalities through week 24. Marked laboratory abnormalities are defined as a shift of 3 or more grades from baseline at some point during the treatment.

Table 8.1.10.5.4.A. Marked Laboratory Abnormalities Through Week 24

	SQV-HGC 600mg N=11	SQV-SGC 400 mg N=12	SQV-SGC 800 mg N=33	SQV-SGC 1200mg N=32
Creatine kinase (high)	0	1	2	1
Glucose (low)	1	0	0	2
Potassium (high)	1	0	1	0
Neutrophils (low)	0	0	1	0

Source: NV15107 (Vol. 67: Table 18)

Table 8.1.10.5.4.B summarizes the marked laboratory abnormalities through week 48. Three events of increased CK values, and one increase in AST value was noted after week 24. Therefore, only a minimal number of laboratory changes occurred through week 48 for saquinaivr SQV-SGC in combination with a variety of antiretroviral regimens

Table 8.1.10.5.4.B. Marked Laboratory Abnormalities Through Week 48

	SQV-HGC 600mg N=11	SQV-SGC 400 mg N=12	SQV-SGC 800 mg N=33	SQV-SGC 1200mg N=32
Creatine kinase (high)	0	2	3	2
Glucose (low)	1	0	0	2
Potassium (high)	1	0	1	0
AST (high)	0	0	0	1
Neutrophils (low)	0	0	1	0

Source: NV15107

Listed below are the individual patient summaries for marked laboratory abnormalities.

Hematology

With regards to hemoglobin, neutrophil and platelet counts, there were no patients with marked laboratory abnormalities.

One patient had a marked laboratory abnormality during the 24 week extension phase.

800 mg SQV-SGC:

> Patient 16327/0091, a 36 year old female had high baseline value of 80% for total neutrophil count (3.4 total absolute value). The total neutrophil count was low on study day 36 and on study day 64 a grade 3 toxicity was observed with total neutrophil count 32% (0.6 absolute value). On study day 120 total neutrophil count was 37% (0.9 absolute value)-grade 2 toxicity. The patient was switched to 1200 mg SQV-SGC on day 120.

Biochemistry

One patient during the first eight weeks of therapy had a marked laboratory abnormality.

400 mg SQV-SGC

> Patient 16326/0076: a 33 year old male had a low CK level of 41 U/L on day 1. At weeks 2 and 4, CK levels were within the normal range of 54-186 UL. On week 8, a grade 4 toxicity value of 3468U/L was recorded.

Seven patients had marked laboratory abnormalities between weeks 8 and 24. These are summarized below:

600 mg SQV-HGC

Patient 16327/0092: a 44 year old male had normal glucose values until day 113 when he had an isolated glucose decrease (grade 3) of 39 mg/dL. This patients also had a potassium increase to 6.5 mEq/L on study day 74. Previous levels had been satisfactory. A repeat on study day 113 still showed a grade 3 toxicity at 6.9 mEq/l, and subsequently returned to normal on day 120. The patient was switched to 1200 mg SQV-SGC on day 176.

800 mg SQV-SGC

Patient 16326/0079: a 42 year old male had normal CK values up to study day 66, when a CK level of 1935 U/L (grade 4) was observed. Subsequent values were within the normal range. The patient was switched to 1200 mg SQV-SGC on study day 101.

Patient 16338/0063: a 36 year old male had a grade 1 CK of 242 at baseline. On study day 57 a CK of 1705 (grade 4) was observed. Subsequent values were within normal range. The patient was switched to 1200 mg SQV-SGC on study day 113.

Patient 16327/0095: a 32 year old male had normal potassium values until study day 70 when an isolated increase to 6.9 mEq/L (grade 3) was observed. This patient did not switch to 1200 mg SQV-SGC.

1200 mg SQV-SGC

Patient 16248/0009: a 37 year old male entered the study with a high baseline value for CK (grade 1 toxicity) of 348 U/L. On study day 113 the CK had risen to 1580 U/L (grade 4).

Patient 1537/0093: a 30 year old male had normal glucose values until study day 37 when an isolated fall to 36 mg/dL (grade 3) was observed.

Patient 16337/0107: a 50 year old male had normal glucose values until study day 28 when an isolated fall to 35 mg/dL (grade 3) was observed.

Comment: These marked laboratory abnormalities appeared to be isolated events perhaps due to specimen handling, particularly for the case of increased potassium levels or decreased glucose levels.

A possible dose-relationship in the number of patients experiencing a shift in serum ALT (SGPT) values from grade 0 to 1 was observed during the first eight weeks of therapy (see Table 8.1.10.5.4.C). In addition an increase in the number of grade 0-1 shifts were seen for AST (SGOT) values at week 24 compared to week 8 (see Table 8.1.10.5.4.A). There appears to be little change in the incidence of abnormal ALT values for week 24 compared to week 8.

These findings are difficult to assess because patients were given the option to switch to SQV-SGC 1200mg and add new anti-retroviral therapy between weeks 8-24. Shifts of greater magnitude or at higher grades were not noted during the 24 week extension phase. In addition there were no premature withdrawals due to liver toxicity.

Table 8.1.10.5.4.C. Number of Patients with Grade 0-1 Shift of ALT/AST Shift (Weeks 8 and 24)

Treatment Group	SQV-SGC 600mg N=11	SQV-SGC 400mg N=12	SQV-SGC 800mg N=33	SQV-SGC 1200mg N=32
Week 8				
ALT	0	1	3	6
AST	1	1	1	1
Week 24				
ALT	0	2	6	8
AST	1	1	4	6

Source: NV15107

In addition to the possible dose-relationship in the number of patients experiencing a shift in serum ALT values, there was an increase in the number of patients originally randomized to SQV-SGC 1200 mg treatment who experienced a 0-1 shift in bilirubin between weeks 24 and 48. There was a minimal change in AST and ALT levels in these patients. More patients experienced low grade shifts in ALT throughout the study compared to AST. Only one patient experienced a laboratory 0-3 grade shift in AST. There were no premature withdrawals through week 24 due to liver toxicity.

Table 8.1.10.5.4.D displays the number and percentage of patients with grade 2,3 and 4 laboratory abnormalities for CK, Glucose increase, AST, ALT, and total bilirubin, respectively.

Table 8.1.10.5.4.D. Summary of Patients with Grade 2 to 4 Shift for CK, Glucose, AST, ALT, and Bilirubin

	SQV-HGC 600mg N=11	SQV-SGC 400 mg N=12	SQV-SGC 800 mg N=33	SQV-SGC 1200mg N=32
CK (increase) Total Grade 3/4	4 (36.4%) 0	5 (41.6%) 3 (25.0%)	8 (24.2%) 4 (12.1%)	4 (12.9%) 3 (9.7%)
Glucose (increase) Total Grade 3/4	1 (9.1%) 1 (9.1%)	1 (8.3%) 1 (8.3%)	3 (9.1%) 0	3 (9.7%) 2 (6.5%)
AST (increase) Total Grade 3/4	1 (9.1%) 0	1 (8.3%) 0	1 (3.0%) 0	3 (9.7%) 1 (3.2%)
ALT (increase) Total Grade 3/4	1 (9.1%) 1 (9.1%)	0 0	2 (6.1%) 0	4 (12.9%) 0
Bilirubin (increase) Total Grade 3/4	0 0	2 (16.7%) 0	1 (3.0%) 0	2 (6.5%) 1 (3.2%)

Source: NV15107

Although triglyceride/cholesterol levels were not protocol-defined laboratory tests in this study, there was concern with the elevated levels seen during the trial. The sponsor was requested to provide the number of patients with grade 2,3 and 4 laboratory abnormatlies for triglycerides, cholesterol, LDL and HDL. As shown in Table 8.1.10.5.4.E, by 48 weeks of therapy, there were 4 patients with grade 3 elevations in the saquinavir SQV-SGC 1200mg group compared to one patient in the SQV-SGC 800 mg and one patient in the SQV-SGC 400 mg cohort. The sponsor states that dose comparisons are difficult to assess because patients in the lower dose groups of SQV-SGC were given the option to switch to SQV-SGC 1200 mg and triglycerides were measured later in the study after which many patients had already switched to SQV-SGC 1200 mg.

Table 8.1.10.5.4.E. Summary of Patients with Grade 2 to Grade 4 Hypertriglyceridemia (48 Weeks)

	SQV-HGC 600mg N = 7	SQV-SGC 400 mg N = 10	SQV-SGC 800 mg N = 25	SQV-SGC 1200mg N = 25
Grade 2	2 (28.6%)	0	3 (12.0%)	6 (24.0%)
Grade 3	0	1 (10.0%)	1 (4.0%)	4 (16.0%)
Grade 4	0	0	0	1 (4.0%)

Source: NV15107

Table 8.1.10.5.4.F shows the number of patients experiencing grade 1-3 cholesterol abnormalities. In this analysis the sponsor used the suggested cut-off levels from the American Heart Association. The sponsor also stated that these samples were not drawn during the fasted state and the values specified for cholesterol are not "normals". These values represent desirable levels that have been associated with low risk of cardiovascular disease. Twenty to 44% of patients had at least one cholesterol value greater than grade 1 and four patients had at least one value greater than grade 2. Again, dose comparisons are difficult to interpret because patients in the lower dose groups of SQV-SGC were given the option to switch to SQV-SGC 1200 mg and cholesterol levels were measured later in the study after which many patients had already switched to SQV-SGC 1200 mg. In addition, the sponsor stated that many patients who had elevated cholesterol did not have low HDLs, or did not have them at the same timepoints as

when they had high cholesterol. The sponsor also emphasized that high cholesterol with normal or high HDLs implies a lower cardiovascular risk compared with high cholesterol and low HDLs.

Table 8.1.10.5.4.F. Summary of Patients with Grade 1 to Grade 3 Elevation of Cholesterol Levels

	SQV-HGC 600mg N = 7	SQV-SGC 400 mg N = 10	SQV-SGC 800 mg N = 25	SQV-SGC 1200mg N = 25
Cholesterol				
Grade 1	3 (42.9%)	2 (20.0%)	7 (28.0%)	11 (44.0%)
Grade 2	1 (14.3%)	1 (10.0%)	1 (4.0%)	2 (8.0%)
Grade 3	0	0	0	0
HDL-cholesterol				
Grade 1	6 (85.7%)	6 (60.0%)	16 (64.0%)	17 (68.0%)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
LDL-cholesterol				
Grade 1	1 (14.3%)	1 (10.0%)	8 (33.3%)	9 (42.9%)
Grade 2	1 (14.3%)	1 (10.0%)	1 (4.2%)	1 (4.8%)
Grade 3	0	0	0	0

Source: NV15107

8.1.10.5.5. Overdosage Exposure

There were no cases of SQV overdose during the study period.

8.1.11. CONCLUSIONS

8.1.11.1. Efficacy

8.1.11.1.1. Eight-week Treatment Period

Based on changes from baseline in plasma HIV RNA the sponsor concluded that the 1200 mg SQV-SGC dose was consistently better over the 8 week treatment period compared to the other dosing groups. The majority of subjects experienced a peak drop in HIV RNA at week 3 with a median change of -1.43 log_{10} copies/mL. In addition, many patients still had a reduction in plasma HIV RNA at week 8 with a median change of 0.64 log_{10} copies/mL at the end of 8 weeks for the 1200 mg SQV-SGC cohort. The sponsor also noted that there was no separation between the 800 mg and 1200mg SQV-SGC groups with respect to CD4 cell counts.

8.1.11.1.2. Twenty-Four Week Extension Period

Overall, 63/80, 78.8% of the patients who had an assessment at week 16 or 24 had a decrease in plasma HIV-RNA accompanied with an increase in CD4 cell counts. Due to the design of the study it was not possible to evaluate the effect caused by the switch from low doses of saquinavir to 1200 mg SQV-SGC.

8.1.11.2. Safety

Saquinavir was generally well tolerated throughout this study. The adverse events most frequently reported were diarrhea, abdominal pain/discomfort, nausea, dyspepsia, headache, fatigue, rash and anxiety. Patients randomized to the 800 mg SQV-SGC group had a higher incidence of gastrointestinal events than those patients randomized to 1200 mg SQV-SGC group. In addition the majority adverse events coded as "anxiety" were reported in the 1200 mg SQV-SGC group.

Twelve patients had a total of 26 serious adverse events during the study. Five patients had serious adverse events considered remotely, possibly or probably related to study drug. The serious events that were considered related to saquinavir were primarily symptoms of gastrointestinal distrubance. There were no deaths at the time of database closure for the 48 week analysis.

A total of 40 patients withdrew from study prior to week 48. Of the 40 patients, twenty withdrewn due to adverse events, two of which were serious. These serious adverse events included gastritis and abdominal pain and discomfort. Non serious adverse events leading to study withdrawal included gastrointestinal

toxicities, (nausea, vomiting, gastritis, diarrhea, abdominal pain/discomfort), rash, fatigue, headache, dizziness, myopathy, arthralgia, weight loss, numbness and musculoskeletal pain.

A total of 12 episodes of marked laboratory abnormalities were observed through week 48. These abnormalities included increases in CK values (7), decreases in glucose levels (3), an increase in serum potassium (1), a increase in AST (1) and a decrease in neutrophil count (1). There appeaeds to be a possible dose-relationship in the number of patients experiencing a shift in serum ALT values from grade 0 to 1 during the eight week monotherapy portion of the study. There was little change in the frequency of these values for week 24 compared to week 8. However, there appeared to be an increase in the number of grade 0 to 1 shifts in AST values at week 24 compared to week 8. There also appeared to be a grade 0 to grade 1 shift in bilirubin between weeks 24 and 48 for those patients originally randomized to the saquinavir SQV-SGC 1200 mg cohort. It is important to note that these findings are difficult to interpret because patients were given the option to switch from low doses of SQV-SGC or SQV-HGC to 1200mg SQV-SGC and to add new antiretroviral agents.

8.2. Protocol NV15182

8.2.1. Protocol Title

A multicenter, open-label study of the safety and activity of saquinavir soft gelatin capsule formulation in combination with other antiretroviral drugs.

8.2.2. Objectives

The primary objective of this study was to evaluate the safety and, secondarily, to determine the antiviral activity of SQV-SGC 1200 mg TID in combination with other antiretroviral drugs for a study period of at least 1 year.

8.2.3. Study Design

The study was to be conducted at 35 to 40 centers in the U.S. and Canada with each center accruing a minimum of nine patients. A total of 400 HIV-infected patients were to be enrolled to provide 340 evaluable patients, assuming a 15% dropout rate. All patients were given SQV-SGC 1200 mg TID either as monotherapy or in combination with antiretroviral drugs of choice. Each patient was to complete at least 52 weeks (1 year) of treatment. Following the completion

of one-year treatment period, patients were allowed continued therapy until commercial availability of SQV-SGC or study termination. The duration of the study was expected to last approximately 64 weeks. Patients would be assessed as shown in schedule of assessments (Table 8.2.3)

Patients were to be stratified at entry by previous history of protease inhibitor use and by CD4 cell count; i.e., 0-100 cells/mm^3, 101-250 cells/mm^3, and greater than 250 cells/mm^3.

Table 8.2.3. Schedule of Assessments

| | Screen | Study Treatment Period | | | | | | | | | | Off-therapy visit |
| | Days -3 to -1 | Day 1 | Weeks | | | | | | | | | |
			2	4	8	12	16	24	36	48	60 or last visit	
Informed consent	X											
Medical history	X											
Physical examination	X	( )										
Height		X										
Weight		X	X	X	X	X	X	X	X	X	X	X
Serum/Urine β-HCG(a)	X											
Chest X-ray	X											
EKG (b)	X											
HIV serology	X											
Hepatitis B/C screen	X											
CD4, CD4%, absolute lymphocyte count	X	X		X	X	X	X	X	X	X	X	
HIV RNA (PCR)	X			X	X		X	X	X	X	X	
Viral resistance		X			X			X	X		X	
Hematology/serum chemistry	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X										
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X

(a) For female patients only, within 14 days of treatment. Repeat for secondary amenorrhea during therapy.
(b) EKG for patients with history of heart disease, or IV drug use, or patients ≥ 45 years.
(Source: Protocol NV15182)

Reviewer's Comment

The study accrued more patients than originally planned. A total of 442 patients were enrolled in 38 centers for this study.

8.2.4. Patient Population

The entry criteria were broad to facilitate rapid accrual of patients. There were no restrictions based on CD4 cell counts or plasma HIV RNA levels. The study planned to include both protease-inhibitor naive and protease-inhibitor experienced patients in a ratio of 3:1. The inclusion and exclusion criteria otherwise were similar to those of protocol NV15107 (see section 8.1.4).

8.2.5. Concomitant Medication

Patients were allowed to combine SQV-SGC with concomitant antiretroviral therapy in this trial with the exception of delavirdine due to a potential pharmacokinetic interaction. The use of nevirapine was also restricted. The use of other protease inhibitors was excluded. Patients who had been on other protease inhibitors had to undergo a 5-day washout period before study day 1.

Since SQV metabolism was shown to be mediated by CYP3A4 isoenzyme, inhibition of drugs metabolized by this same pathway could potentially occur. Therefore, patients were not allowed to take cisaspride, triazolam, terfenadine, astemizole due to possible increased plasma concentrations. Ketoconazole, clarithromycin and erythromycin were restricted since these drugs were shown to increase SQV levels due to their inhibitory effect on hepatic metabolism. Rifampin and rifabutin were previously shown to decrease SQV plasma concentrations due to their induction of hepatic enzymes. For the same reason, the use of carbamazepine, phenytoin, phenobarbitol and nevirapine was restricted.

8.2.6. Treatment Compliance

The assessment of treatment compliance is similar to that of protocol NV15107 (see section 8.1.6).

8.2.7. Endpoints

The endpoints of this study were safety and efficacy of treatment to be evaluated at week 24. The safety parameters, adverse events and laboratory test evaluations, and efficacy parameters, quantitative HIV RNA and CD4 cell count, of

this protocol were similar to those of protocol NV15107 (see section 8.1.7).

8.2.8. Premature Discontinuation of Treatment

Patients could voluntarily withdraw from the study at any time for any reason. The investigator also had the right to withdraw patients from the study due to adverse events, intercurrent illness, treatment failure, protocol violation, laboratory toxicity, or any other administrative reasons.

Reviewer's Comment

The sponsor did not define criteria for "treatment failure" with regard to virologic (HIV RNA level) or immunologic (CD4 cell count) results. The decision to withdraw patients based on treatment failure was left to the investigators' choice.

8.2.9. Analytical and Statistical Plans

A planned 24-week descriptive analysis of safety data, laboratory data, and efficacy data was to be conducted, followed by a 48-week safety update.

The sponsor proposed that all patients who had at least one dose of test treatment and safety follow-up information would be included in the safety analysis. The sponsor also proposed that patients without a baseline or a follow-up efficacy parameter would be excluded from the analysis of that parameter only.

Clinical adverse events would be described with frequency tables categorized by treatment as well as relationship to treatment and severity. Laboratory safety data including shift tables from baseline, summary of worst values and grade 3/4 abnormalities would be evaluated. The sponsor did not plan to conduct formal statistical tests on safety data.

Since this was primarily a safety study, the sponsor did not plan to conduct formal statistical tests on efficacy data. Data on CD4 cell counts and HIV RNA levels would be summarized descriptively (listings and tables) in terms of absolute changes from baseline as well as AUCMB and DAVG analyses over the treatment period. The sponsor would provide tables containing mean, median, minimum, maximum, and interquartile range for HIV RNA and CD4 changes.

Descriptive subgroup analyses were to be conducted with regard to CD4 cell count strata (0-100 cells/mm^3; 101-250 cells/mm^3; >250 cells/mm^3), and history of previous protease inhibitor treatment.