8.2.10. Results

8.2.10.1. Patient Disposition

The study was opened for patient accrual on 4/19/96 and accrual was completed on 7/4/96. Of the 444 patients entering the study, two patients did not return for any follow-up visits after receiving trial medication and were excluded from analysis for safety and efficacy. Of the remaining 442 evaluable patients, 382 completed up to 24 weeks of treatment (cutoff date for data analysis), 60 prematurely withdrew from the study. The sponsor provided reasons for early withdrawals as follows:

- 21 patients due to adverse events/intercurrent illness
- 16 due to refused treatment/non cooperation/withdrew consent
- 13 due to insufficient therapeutic response
- 4 due to laboratory toxicity
- 4 due to loss of follow-up
- 1 due to miscellaneous reason
- 1 death while on therapy

The disposition of patients including premature withdrawals as presented by the sponsor's and FDA reviewer's analyses is presented in Table 8.2.9.1.

Table 8.2.9.1. Summary of Patient Disposition

Patient Disposition	Number of Patients		
	Sponsor's Analysis	FDA Reviewer's Analysis	
			(%)
Randomized	444	444	
Evaluable	442	442	
Premature withdrawals			
- adverse event/intercurrent illness	21	27	(6.1)
- refusal of treatment/noncompliance/ withdrawal of consent	16	12	(2.7)
- insufficient therapeutic response	13	13	(2.9)
- laboratory toxicity	4	3	(0.7)
- lost to follow-up	4	4	(0.9)
- death on therapy	1	1	(0.2)
- miscellaneous	1	0	-
- Death off therapy	2	2	(0.5)

(Source: NV15182)

Reviewer's Comments

1. There were no pre-defined criteria of treatment failure (i.e., in terms of CD4 counts, plasma HIV RNA levels, and/or progression of disease) in the original protocol (see section 8.2.8). The decision to discontinue patients on the basis of "insufficient therapeutic response" was left to the discretion of the investigators. Therefore, criteria for treatment failure varied greatly from center to center which probably reflected the diversity of clinical practice. Several examples are given below.

- *Patient 17050/2406, a 44-year-old male, had progressive HIV RNA decreases from baseline of 8050 to 1815 copies/mL (-0.64 log_{10}) for approximately 8 weeks. His CD4 counts remained unchanged from a low baseline of approximately 7 cells/mm^3. While immunological response was not demonstrated, the patient had some virologic suppression. However, he was taken off the study on day 120 due to "insufficient therapeutic response."*

- *Patient 17167/2915, a 39-year-old male, had a baseline CD4 count of 80 cells/mm^3 and HIV RNA of 1435 copies/mL. The CD4 counts for week 4, 8, 16 and 24 time points were 240, 220, 210, 260 cells/mm3 and 741, 245, 6530, 173 copies/mL for HIV RNA levels, respectively. His treatment was discontinued after week 16 (day 141) due to "insufficient therapeutic response." The single elevated HIV RNA level of 6530 copies/mL could have been an laboratory error, a transient change in the patient's immune status, or noncompliance.*

- *Patient 17187/2890, a 48-year-old male, had baseline CD4 count of 100 cells/mm^3 and HIV RNA of 1711 copies/mL. He was discontinued on day 69 due to "insufficient therapeutic response," two days prior to the availability of CD4 and HIV RNA data which showed a trend of virological and immunological improvements (1374 copies/mL and 156 cells/mL, respectively) from the previous levels (3345 copies/mL and 107 cells/mL, respectively) at week 8.*

2. The reason for premature discontinuation of patient 16988/2422 was listed as "miscellaneous" in the protocol report. The CRS form listed the reason as "lack of compliance" and is thus reclassified by this reviewer.

3. Patient 17196/2733 withdrew from treatment due to intercurrent cholangitis secondary to cholelithiasis with elevated alkaline phosphatase (grade 2) and

transaminases (grade 1). The investigator initially attributed the reason for early withdrawal as "laboratory toxicity." Subsequently, the sponsor reclassified this case as "adverse event/intercurrent illness" (see also Reviewer's Comment #2, section 8.2.10.4.4.3). This reviewer agreed with the latter classification.

4. A number of early withdrawals were classified under "refused treatment/non-compliance/withdrew consent" by the investigators/sponsor. However, a review of CRS reports on these cases showed a close temporal relationship between significant adverse events experienced by the patients at the time of treatment discontinuation. Without evidence to the contrary, this reviewer reclassified the reason for premature withdrawal as due to "adverse events." The following cases were reclassified:

- *Patient 17002/2535 developed moderate abdominal cramps, nausea and vomiting while on SQV. He elected to discontinue SQV on day 40 and all symptoms resolved within one day. Of note, the sponsor subsequently reclassified this case as secondary to "adverse event" in the 48-week analysis.*

- *Patient 17166/2932 had mild abdominal discomfort ("probable" relationship to test drug as assessed by the investigator) for 47 days. The symptom resolved 5 days after discontinuation of SQV.*

- *Patient 17187/2893 experienced moderate headache ("possible" relationship to treatment) and severe diarrhea ("possible") starting on study days 2 and 6, respectively. The headache promptly resolved after drug discontinuation on day 16. No additional data were provided on the resolution of diarrhea.*

- *Patient 17165/2978 had ongoing moderate abdominal discomfort, nausea, vomiting and gas considered probably related to study drug. He also experienced moderate fatigue thought to be remotely related to treatment. He was discontinued from the study on day 153.*

- *Patient 16993/2272 discontinued on day 71. At the time he was noted to have acute hepatitis B infection with markedly elevated transaminases (ALT > 2000 U/L, AST > 1000 U/L). The investigator attributed the reason for premature discontinuation as (1) adverse event/intercurrent illness and (2) failure to return. The sponsor subsequently classified the reason as "refused treatment/noncompliance/withdrew consent." The records, however, indicated that this patient returned at least 8 times for follow-up visits.*

8.2.10.2. Patients with Protocol Deviation

Although concomitant use of other protease inhibitors was prohibited, 15 patients took concomitant protease inhibitor while on this trial. Nine patients were on indinavir, five on ritonavir and one on SQV-HGC. One patient took delavirdine. The sponsor did not report other protocol violations in this study.

8.2.10.3. Demographic Data

The majority of patients were male (90%) and Caucasian (73%). The age ranged from 15 to 71 years. Table 8.2.10.3.A summarizes the demographic analysis as provided by the sponsor.

Table 8.2.10.3.A. Summary of Demographic Data (N=442)

	NV15182
SEX	
Male	398 (90%)
Female	44 (10%)
RACE	
White	324 (73%)
Black	62 (14%)
Hispanic	39 (9%)
Oriental	8 (2%)
Other	9 (2%)
AGE	
Mean	40.1
Range	15 - 71
HEIGHT (cm)	
Mean	175.0
Range	144 - 196
WEIGHT (Kg)	
Mean	76.3
Range	48 - 128

(Source: NV15182)

A wide range of concomitant diseases were reported in the patient population, none of which were thought to have any significant influence on the course of the trial. The most common concomitant diseases were psychiatric disorders, notably depression (17%), gastrointestinal disorders, and skin disorders. Excluding antiretroviral treatment, antibiotics and chemotherapeutics were the most common

concomitant treatment.

The majority of patients (96%) were antiretroviral experienced. Approximately 18% of patients had previous treatment with a protease inhibitor (Table 8.2.10.3.B)

Table 8.2.10.3.B. Summary of Antiretroviral Treatment History

Treatment history	Number of Patients	
Antiretroviral treatment		
- Naive	18	(4.1%)
- Experienced	424	(95.9%)
Protease inhibitor treatment		
- Naive	363	(82.1%)
- Experienced	79	(17.9%)

(Source: NV15182)

The baseline characteristics of patients in terms of CD4 cell count and HIV RNA level are summarized in Table 8.2.10.3.C. The median CD4 cell count at entry was 201 cells/mm^3 and the median HIV RNA level was 4.25 $\log_{10}$ copies/mL.

Table 8.2.10.3.C. Summary of Baseline CD4 and HIV RNA

Baseline Values	CD4 (cells/mL)	HIV RNA ($\log_{10}$ copies/mm^3)
	n = 442	n = 441
Mean	227	4.14
Standard deviation	164	0.90
Median	201	4.25
Minimum	0	2.30
Maximum	743	6.33
Interquartile range		

(Source: NV15182)

Reviewer's Comments

1. The study population was predominantly Caucasian male (90%). While this distribution of study patients approximated the current percentages of male and female HIV-infected patients (80% and 20%, respectively) in the U.S., it did not

mirror the actual ethnicity characteristics. Future studies should be planned to incorporate a more heterogeneous population to reflect the true picture of patient gender and ethnicity distributions.

2. The study did not enroll pediatric patients under age 15. Data on the safety and efficacy of SQV-SGC in pediatric populations are being addressed in an ongoing pediatric study.

8.2.10.4. Safety Outcomes

The sponsor included all patients with at least one dose of test treatment and safety follow-up information in the safety population. The following safety review is based on 24-week data. The sponsor subsequently submitted a 48-week safety update of this trial. A separate review of the updated safety data is presented in an addendum.

8.2.10.4.1. Drug Exposure

The extent of drug exposure for patients on the study is presented in Table 8.2.10.4.1.A. The number of patients on treatment for 4, 8, 16 and 24 weeks are summarized in Table 8.2.10.4.1.B.

Table 8.2.10.4.1.A. Summary of Duration of Treatment[1]

NV15182	Treatment Duration (days)	Dose/day (mg)	Dose/weight (mg/Kg)
	n = 442	n = 442	n = 439
Mean	177.9	3600	48.4
Standard deviation	49.1		7.7
Median	196.0	3600	47.7
Range			

[1] Cutoff study day 196 is used for all missing end dates
(Source: NV15182)

Table 8.2.10.4.1.B. Summary of Exposure to Study Treatment

Treatment Duration (weeks)	Number of Patients
4	424 (95.9%)
8	409 (92.5%)
16	397 (89.8%)
24	382 (86.4%)

(Source: NV15182)

8.2.10.4.2. Adverse Events

8.2.10.4.2.1. Overview of Adverse Events

The following section focuses primarily on the clinical adverse events reported in the study population. Approximately 91% of patients (n=403) experienced at least one adverse event during the 24-week study period. A number of these patients had more than one occurrence of the same adverse events, or more than one concomitant adverse event.

The most common treatment-emergent adverse events experienced by the study population were gastrointestinal disorders. Diarrhea occurred in 39.1% of patients, nausea in 24.7%, and dyspepsia in 17.6%. Abdominal complaints ranging from "discomfort" to "pain" and "colic" were experienced in approximately 25% of study patients. Other clinically significant adverse events of lower frequency, were headache (14.7%), fatigue (13.8%), and skin rash (10.0%). Notable psychiatric disorders were insomnia (4.5%), depression (4.5%), and anxiety (3.6%).

Overall, the majority of adverse events were of mild to moderate intensity. Diarrhea and nausea were the most frequently reported gastrointestinal adverse events. Approximately 43% of patients had mild diarrhea (3 to 4 loose stools per day, transient or less than 1 week in duration), 28% with moderate diarrhea (5 to 7 loose stools per day, lasting over 1 week), and 3% with severe diarrhea (more than 7 loose stools per day, orthostatic hypotension, or requiring IV intervention). There was 1 case of life-threatening diarrhea possibly complicated by pseudomembranous colitis. Twenty-five percent of patients had diarrhea of unknown intensity. More than half of the patients experienced mild nausea, 23% with moderate, and 4% with of severe symptoms. Cases of mild, moderate and severe abdominal pain were reported in approximately 46% , 20%, and 8% of patients, respectively. Most of the complaints of headache and fatigue appeared

equally distributed in the mild and moderate categories.

Data on treatment-emergent adverse events are analyzed by this reviewer and presented in the following Tables. Table 8.2.10.4.2.1.A summarizes the adverse events that were reported in at least 2% or more of all patients. Table 8.2.10.4.2.1.B summarizes the adverse events by intensity reported in ≥2% of patients, excluding those considered "unrelated" to treatment by the investigators. Table 8.2.10.4.2.1.C summarizes only those adverse events considered related to treatment and of at least moderate intensity occurring in 2% or more of patients.

Table 8.2.10.4.2.1.A. Summary of Patients with Treatment-Emergent Adverse Events Reported in ≥2% of Patients

Body System /Disorder	Number of Patients			
	Total (N = 442)		Excluding those unrelated to Trial[1]	
	n	(%)	n	(%)
Body as a whole				
Abdominal discomfort	75	(17.0)	72	(16.3)
Headache	65	(14.7)	51	(11.5)
Fatigue	61	(13.8)	47	(10.6)
Abdominal pain[2]	35	(7.9)	30	(6.8)
Fever	29	(6.6)	9	(2.0)
Night sweats	22	(5.0)	12	(2.7)
Decreased appetite	16	(3.6)	10	(2.3)
Trauma	14	(3.2)	2	(0.5)
Weight loss	14	(3.2)	5	(1.1)
Asthenia	9	(2.0)	7	(1.6)
Gastrointestinal				
Diarrhea	173	(39.1)	152	(34.4)
Nausea	109	(24.7)	96	(21.7)
Dyspepsia	78	(17.6)	77	(17.4)
Flatulence	42	(9.5)	41	(9.3)
Vomiting	31	(7.0)	26	(5.9)
Constipation	17	(3.8)	14	(3.2)
Buccal mucosa ulceration	10	(2.3)	6	(1.4)
Central & peripheral nervous				
Dizziness	17	(3.8)	8	(1.8)
Extremity numbness	16	(3.6)	9	(2.0)
Peripheral neuropathy	14	(3.2)	10	(2.3)
Paresthesia	10	(2.3)	5	(1.1)
Dermatological				
Rash	46	(10.4)	19	(4.3)
Pruritus	19	(4.3)	11	(2.5)
Skin disorder (NOS)	10	(2.3)	4	(0.9)
Musculoskeletal				
Arthralgia	15	(3.4)	11	(2.5)
Myalgia	13	(2.9)	9	(2.0)
Musculoskeletal pain	13	(2.9)	6	(1.4)
Respiratory				
Sinusitis	27	(6.1)	6	(1.4)
Rhinitis	22	(5.0)	1	(0.2)
Cough	21	(4.8)	5	(1.1)
Bronchitis	16	(3.6)	3	(0.7)
Pharyngitis	13	(2.9)	3	(0.7)
Allergic rhinitis	9	(2.0)	1	(0.2)
Dyspnea	9	(2.0)	3	(0.7)

(continuing...)

Table 8.2.10.4.2.1.A. (Cont.) Summary of Patients with Treatment-Emergent Adverse Events Reported in ≥2% of Patients

Body System /Disorder	Number of Patients			
	Total (N = 442)		Excluding those unrelated to Trial[1]	
	n	(%)	n	(%)
Psychiatric				
Depression	20	(4.5)	10	(2.3)
Insomnia	20	(4.5)	15	(3.4)
Anxiety	16	(3.6)	7	(1.6)
Resistance mechanism				
Upper resp. tract infection	25	(5.7)	4	(0.9)
Influenza	21	(4.8)	4	(0.9)
Herpes simplex	20	(4.5)	3	(0.7)
Herpes zoster	9	(2.0)	3	(0.7)
Miscellaneous				
Visual disturbance	9	(2.0)	3	(0.7)
Taste alteration	9	(2.0)	8	(1.8)
Micturition	11	(2.5)	5	(1.1)

[1] Includes adverse events of unknown relationship to treatment.
[2] Includes "abdominal pain" and "colic abdomen" as coded by the sponsor.
NOS: not otherwise specified by sponsor.
(Source: FDA Reviewer's analysis of NV15182)

Table 8.2.10.4.2.1.B. Summary of Treatment-Emergent Adverse Events[1] Classified by Intensity Reported in ≥2% of Patients

Body System/Disorder	Total (N = 442)		Mild		Moderate		Severe		Life-threatening		Unknown Intensity[2]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Body as a whole												
Abdominal discomfort	72	(16.3)	34	(7.7)	16	(3.6)	5	(1.1)	-		17	(3.8)
Headache	51	(11.5)	18	(4.1)	18	(4.1)	2	(0.5)	-		13	(2.9)
Fatigue	47	(10.6)	18	(4.1)	14	(3.2)	2	(0.5)	-		13	(2.9)
Abdominal pain[3]	30	(6.8)	13	(2.9)	5	(1.1)	3	(0.7)	-		9	(2.0)
Night sweat	12	(2.7)	8	(1.8)	2	(0.5)	-		-		2	(0.5)
Decreased appetite	10	(2.3)	5	(1.1)	3	(0.7)	-		-		2	(0.5)
Gastrointestinal												
Diarrhea	152	(34.4)	66	(14.9)	42	(9.5)	5	(1.1)	1	(0.2)	38	(8.6)
Nausea	96	(21.7)	52	(11.8)	22	(5.0)	4	(0.9)	-		18	(4.1)
Dyspepsia	77	(17.4)	40	(9.0)	15	(3.4)	1	(0.2)	-		21	(4.7)
Flatulence	41	(9.3)	17	(3.8)	7	(1.6)	3	(0.7)	-		14	(3.2)
Vomiting	26	(5.9)	13	(2.9)	9	(2.0)	1	(0.2)	-		3	(0.7)
Constipation	14	(3.2)	5	(1.1)	2	(0.5)	-		-		7	(1.6)
Dermatological												
Rash	19	(4.3)	10	(2.3)	4	(0.9)	-		-		5	(1.1)
Pruritus	11	(2.5)	4	(0.9)	4	(0.9)	-		-		3	(0.7)
Psychiatric												
Insomnia	15	(3.4)	6	(1.4)	4	(0.9)	-		-		5	(1.1)
Depression	10	(2.3)	2	(0.5)	2	(0.5)	-		-		6	(1.4)
Musculoskeletal												
Arthralgia	11	(2.5)	4	(0.9)	-		-		-		7	(1.6)
Myalgia	9	(2.0)	3	(0.7)	-		-		-		6	(1.4)
Peripheral nervous												
Peripheral neuropathy	10	(2.3)	2	(0.5)	-		-		-		8	(1.8)
Extremity numbness	9	(2.0)	2	(0.5)	1	(0.2)	-		-		6	(1.4)

[1] Includes adverse events of unknown relationship to treatment.
[2] Unspecified by investigators.
[3] Includes "abdominal pain" and "colic abdomen" as coded by sponsor.
(Source: FDA Reviewer's analysis of NV15182)

Table 8.2.10.4.2.1.C. Summary of Patients with Treatment-Emergent Adverse Events[1] of at least Moderate Intensity Occurring in ≥2% Patients (N=442)

Body System/Disorder	Number of Patients	
	n	(%)
Body as a whole		
Abdominal discomfort	38	(8.6)
Headache	33	(7.5)
Fatigue	29	(6.6)
Abdominal pain	17	(3.8)
Gastrointestinal		
Diarrhea	86	(19.5)
Nausea	44	(9.9)
Dyspepsia	37	(8.4)
Flatulence	24	(5.4)
Vomiting	13	(2.9)
Constipation	9	(2.0)
Psychiatric		
Insomnia	9	(2.0)
Dermatological		
Rash	9	(2.0)

[1] Includes adverse events related to treatment, of unknown intensity and/or relationship to treatment.
(Source: FDA Reviewer's analysis of NV15182)

Reviewer's Comments

1. Although the protocol provided guidance for assessing and categorizing the causal relationship between an adverse event and test medication (i.e., unrelated, remote, possible, and probable), the interpretation of these guidelines was entirely up to the individual investigator's opinions; hence, the causality assessments were subjective. However, the criteria for each category were reasonably clear for relatively uniform assessments by various investigators that the sponsor's summaries of adverse events and their relationship to trial treatment were acceptable.

2. A number of patients had adverse events in which either relationship to treatment or intensity was not described by the investigators. These patients were not accounted for by the sponsor in the final tallies. This reviewer included these cases in the calculation for Tables 8.2.10.4.2.1.A, 8.2.10.4.2.1.B and 8.2.10.4.2.1.C as indicated in the legends. In response to FDA requests, the sponsor has recently submitted new tabulations of adverse events to include these cases.

3. The sponsor classified abdominal-related complaints as "discomfort," "pain" and "colic abdomen." This reviewer classified complaints of "abdominal pain" and "colic abdomen" as "abdominal pain." "Abdominal discomfort" remained a separate category.

4. Under "dermatological disorders", for the lack of further specific details, this reviewer classified cases of "papular rash" and "pruritic rash" under the general category of "rash."

8.2.10.4.2.2. Serious and Life-Threatening Adverse Events

The sponsor reported 36 patients with serious adverse events in 24 weeks of study. Some of these patients had more than one event. Three of these serious adverse events were thought by the investigators to have "possible" or "probable" relationship with treatment and 2 with "remote" relationship. One patient had life-threatening diarrhea. These cases are summarized as follows:

- Patient 16998/2707, a 50-year-old male, suffered a transient ischemic attack on day 4, and was thought to be "severe" but remotely related to treatment by the investigator. He stopped study medication on day 8 with reason given as "refused treatment/non-cooperation."

- Patient 17050/2403, a 43-year-old male, was hospitalized on study day 76 for moderate herpes zoster infection, thought to be remotely related to treatment.

- Patient 17165/2980, a 16-year-old hemophiliac, had a severe allergic reaction (not otherwise specified) for 71 days in duration starting on study day 14, thought to be remotely associated with the test drug. On day 44 he developed cerebral hemorrhage thought to be life-threatening and to have "possible" relationship with treatment by the investigator. Both events resolved without sequelae according to the records.

- Patient 16980/2300, a 49-year-old male, had severe diarrhea and moderate vomiting from the first study day which resulted in his premature withdrawal from the study on day 34. The diarrhea stopped two days later. The investigator reported the diarrhea as "serious" and possibly related to treatment.

- Patient 17193/2864 was a 45-year-old male who had "life-threatening" diarrhea that prompted his early treatment discontinuation. No further clinical details of the diarrhea were recorded on the CRF. The test drug was attributed as the "probable" cause of the diarrhea, although the investigator also implied pseudomembranous colitis as a "possible" cause. Bacteriologic culture was negative. No information regarding microbial toxin assay was provided.

8.2.10.4.2.3. Adverse Events Associated with Premature Discontinuation of Treatment

According to the sponsor, 21 patients withdrew prematurely from the study by week 24 due to adverse events, 4 to laboratory toxicities, and 1 died while on therapy. However, the analysis by this reviewer shows 27 withdrawals as a result of adverse events (see section 8.2.10.1 and Table 8.2.10.1). The distribution of patients with adverse events at the time of withdrawal (excluding laboratory toxicity cases to be discussed later) and the intensity relationship of these adverse events were analyzed and summarized by this reviewer in Table 8.2.10.4.2.3.

Although a number of patients experienced multiple adverse events, the most frequent reasons of premature discontinuation were diarrhea (75%), nausea (41.7%), abdominal pain (41.7%), and vomiting (20.8%). The majority of these adverse events were of moderate to severe intensity. Other adverse events of note are also listed below.

- Patient 16985/2100 was a 34-year-old male who presented with epigastric pain at enrollment time. His screening laboratory data revealed alkaline phosphatase of 1075 U/L (grade 4 toxicity), mildly elevated AST, ALT, and normal total bilirubin. He was subsequently diagnosed with sclerosing cholangitis. SQV therapy was discontinued due to intercurrent illness on day 6. The reason for early discontinuation was considered unrelated to treatment.

- Patient 17163/2997 was a 67-year-old male who had no history of previous SQV exposure. On day 5, two hours after taking SQV, the patient experienced fever (38.7°C), hypertension (170/85 mm Hg), and muscle spasms. The adverse event was attributed to a generalized allergic reaction, moderate in intensity, by the investigator. His condition subsequently resolved with no sequelae.

- Patient 17188/2664, a 45-year-old male, experienced increased asthmatic attacks and dyspnea 10 days after being on SQV. The investigator thought that these symptoms were "possibly" related to treatment. The patient also had moderate fatigue, diarrhea, and increased somnolence. With the exception of fatigue, all other symptoms persisted after discontinuation of therapy on day 15.

Table 8.2.10.4.2.3. Summary of Adverse Events[1] Associated with Premature Discontinuation of Treatment (Excluding Laboratory Toxicity)

Adverse Event	Total (N = 24)		Life-threatening		Severe		Moderate		Mild	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Diarrhea	18	(75.0)	1	(4.2)	5	(20.8)	8	(33.3)	4	(16.7)
Nausea	10	(41.7)	-		3	(12.5)	6	(25.0)	1	(4.2)
Abdominal pain	10	(41.7)	-		3	(12.5)	4	(16.7)	3	(12.5)
Vomiting	5	(20.8)	-		1	(4.2)	2	(8.3)	2	(8.3)
Dyspepsia	4	(16.7)	-		-		4	(16.7)	-	
Headache	4	(16.7)	-		-		4	(16.7)	-	
Fatigue	4	(16.7)	-		2	(8.3)	2	(8.3)	-	
Bloating	3	(12.5)	-		2	(8.3)	1	(4.2)	-	
Loss of appetite	2	(8.3)	-		-		1	(4.2)	1	(4.2)
Insomnia	2	(8.3)	-		-		1	(4.2)	1	(4.2)
Anxiety	1	(4.2)	-		-		1	(4.2)	-	
Irritability	1	(4.2)	-		-		1	(4.2)	-	
Depression	1	(4.2)	-		-		1	(4.2)	-	
Disorientation	1	(4.2)	-		-		-		1	(4.2)
Somnolence	1	(4.2)	-		-		1	(4.2)	-	
Allergic reaction	1	(4.2)	-		-		1	(4.2)	-	
Asthma	1	(4.2)	-		-		1	(4.2)	-	
Pruritus	1	(4.2)	-		-		1	(4.2)	-	
Rash	1	(4.2)	-		-		1	(4.2)	-	
Facial/extremity swelling	1	(4.2)	-		-		-		1	(4.2)

[1] Where more than one similar adverse events was reported by a patient, the most severe rating was recorded.
(Source: FDA Reviewer's analysis of NV15182)

Reviewer's Comments

1. The sponsor used the ACTG grading system and its own grading system where applicable to standardize the reporting of adverse events and their severity. The criteria established by these systems are reasonably clear. However, the variabilities of patients' perceptions of toxicities and adverse events were not always taken into account in the grading scheme. Therefore, a clinically graded "moderate" (grade 2) diarrhea (i.e., 5 to 6 stools a day or diarrhea lasting more than 1 week) could conceivably be perceived by a patient as incapacitating enough (i.e., severe) to consider early withdrawal from the study.

2. There were 8 cases (1.8%) of allergic reaction reported in this study. Three cases were thought to be unrelated to study drug, 2 cases with "remote" causal relationship, and 1 case resulting in discontinuation of the study. The relationship to treatment for the last two cases was unknown.

3. A review of CRFs showed that the investigators did not always interpret the reasons for premature discontinuations in a uniform or consistent manner. However, the sponsor subsequently reevaluated and reclassified cases where the investigators' opinions were called into question. This reviewer agrees with the sponsor's final classifications in these cases.

8.2.10.4.3. Death

There were 3 deaths attributable to AIDS or AIDS-related conditions in the safety database at the 24-week analysis. One death occurred while the patient was on SQV treatment, and two occurred after patients discontinued SQV for 13 and 64 days, respectively.

- Patient 16989/2383, a 61-year-old male, developed PCP on study day 10, was hospitalized from day 15 to 39 and died on day 49 while on SQV. The cause of death was AIDS.

- Patient 17002/2535, a 52-year-old male, discontinued SQV on study day 40 after experiencing moderate abdominal cramps ("probable" relationship to test drug), nausea and vomiting ("possible" relationship). He died of AIDS-related progressive multifocal leukoencephalopathy on day 104.

- Patient 17167/2909, a 45-year-old male, had a history of CNS toxoplasmosis. He was hospitalized on study day 9 for disorientation, somnolence, memory loss and anemia. SQV treatment was discontinued on day 16. He died of AIDS on day 29.

Reviewer's Comment

It appears that the three cases of death in this study can be attributable to complications of AIDS. There is no obvious relationship to link these cases to study drug.

8.2.10.4.4. Laboratory Findings

8.2.10.4.4.1. Overview of Laboratory Abnormalities

Significant incidences of low-grade shifts of laboratory parameters (grade 0 to 1) were present in the study population. These included elevated glucose (28.5%), creatine kinase (23.5%), ALT (18.2%), and AST (17.8%). Several other analytes also showed mildly elevated levels, albeit of lower frequency; e.g., amylase (10.9%), total bilirubin (8.7%) and alkaline phosphatase (5.9%). An overview of grade shifts for routine laboratory tests in patients with normal baseline levels (grade 0) is presented in Table 8.2.10.4.4.1.

The sponsor attributed many of the low-grade abnormalities to laboratory artifacts or concurrent clinical conditions of the patients. For example, of the 143 patients with elevated AST and ALT grade 1 or more, 10% were reported to be positive for hepatitis B serology, 21% for hepatitis C, and 2% for both hepatitis B and C at screening. Elevated creatine kinase levels in most patients, according to the sponsor, were thought to be secondary to vigorous exercise by patients prior to blood collection.

Table 8.2.10.4.4.1. Percentage of Patients with Abnormal Laboratory Shifts from Normal Baseline

Analyte	Percentage of Patients			
	0 - 1	0 - 2	0 - 3	0 - 4
↑ Alkaline phosphatase (AP)	5.9	0.9	-	-
↑ AST (SGOT)	17.8	2.2	1.1	0.8
↑ ALT (SGPT)	18.2	4.0	2.1	0.8
↑ Total bilirubin	8.7	0.9	1.2	0.0
↑ Creatine kinase (CK)	23.5	5.2	1.2	1.7
↑ Amylase	10.9	0.8	0.3	-
↑ Glucose	28.5	3.0	0.7	-
↓ Glucose	8.8	6.2	2.4	3.3
↑ Calcium	1.8	-	-	-
↓ Calcium	3.6	0.5	-	-
↓ Phosphate	7.7	1.4	-	-
↑ Creatinine	3.6	0.5	-	-
↑ Potassium	4.3	1.4	-	-
↓ Potassium	2.8	0.2	-	-
↑ Sodium	3.0	-	-	-
↓ Sodium	10.0	0.7	0.2	-

(Source: FDA Analysis of NV15182)

Reviewer's Comments

1. Low-grade elevation of liver function tests (AST, ALT) in the study population mirrored what had been observed in previous studies with SQV-SGC and SQV-HGC. The sponsor presented evidence of concurrent viral hepatitis in about 30% of patients who had increased levels of transaminases. While viral hepatitis might have contributed to the abnormal liver function tests, drug-induced hepatitis cannot be ruled out in these patients. Therefore, patients on SQV-SGC should be routinely monitored for evidence of hepatotoxicity.

2. A significant number of patients on treatment (23.5%) had low-grade shift in creatine kinase. Some patients also experienced markedly elevated levels; e.g., 1.2% with grade 0-3, and 1.7% with grade 0-4 (see section 8.2.10.4.4.2). The sponsor did not provide narratives regarding the clinical conditions of these patients at the time of CK elevation. CK elevation is associated with a number of causes ranging from muscle trauma, myopathies, exercise, therapeutic injection, acute psychiatric diseases, CNS infection or inflammation, seizure, arrhythmia, hypothyroidism, hypokalemia, and alcoholism. In HIV-infected patients, HIV-associated myopathy (inflammatory and noninflammatory) has been reported. Myopathy has also been linked to antiretroviral agents; particularly, ZDV-induced mitochondrial myopathy. These myopathic conditions result in elevated CK levels, with or without clinical manifestations. Without further extensive studies (e.g., muscle biopsy, electromyographic findings, etc.), it is difficult to assess whether the elevated CK levels were secondary to progressing HIV infection or drug toxicity.

3. Elevated AP, mostly low-grade, was present in approximately 7% of patients. In many instances, the rise of AP paralleled increases in AST, ALT, and GGT levels indicative of a cholestatic state. There was one case of cholangitis (patient 16985/2097) and one case of cholelithiasis (patient 16985/2100) which showed significant AP elevations. Although multiple concurrent etiologic factors were probably operative in these patients, it remains to be seen whether SQV-SGC plays a contributory role in cholestasis or cholangitis.

4. Approximately 11% of patients exhibited low-grade (0 to 1) hyperamylasemia for which no attributable causes could be readily discerned. Several patients with "abdominal cramps" had elevated amylase levels. One case of grade 0-3 shift (patient 16985/2097) was seen in the setting of cholangitis. One patient (17050/2401) had "salivary gland enlargement" and persistently elevated amylase (grade 1 to 2) in the course of study. Unexplained, marked elevation of amylase with no effect on clinical outcome has been reported to be prevalent in HIV infection. In fact, asymptomatic hyperamylasemia has been suggested as a marker

of advanced HIV infection. In addition, pentamidine use has also been implicated in hyperamylasemia.

5. The protocol did not specify the collection of fasting blood glucose levels, therefore, the random glucose levels may account for the low-grade elevations. However, hyperglycemia and diabetes mellitus have been recently reported in patients taking protease inhibitors (see section 8.2.10.4.4.2). Hypoglycemia, on the other hand, has been reported in patients taking SQV-HGC as monotherapy (study NV14256). However, laboratory artifacts may account for "hypoglycemia," particularly in the absence of clinical signs and symptoms (see reviewer's comment # 4, section 8.2.10.4.4.2).

6. HIV-infected patients have been reported to have a spectrum of electrolyte and acid-base disturbances; i.e., hyponatremia, hypernatremia, hypokalemia, hyperkalemia, abnormal calcium and phosphate homeostasis, etc.. Among these, hyponatremia (< 130 mEq/L) is quite common in patients with advanced disease. The frequency of hyponatremia ranges from 28.5% to 56% according to several prospective studies in patients with AIDS. The presence of hyponatremia is significantly associated with increased morbidity and may contribute to overall mortality. Excessive gastrointestinal losses, syndrome of inappropriate antidiuretic hormone secretion (SIADH), HIV-associated nephropathy, adrenal insufficiency and concomitant opportunistic infections have been implicated as contributing factors of hyponatremia. Several frequent concomitant medications (high-dose trimethoprim, pentamidine, miconazole, amphotericin, vidarabine) have also been implicated in inducing hyponatremia. Finally hypovolemic hyponatremia can result from diarrhea induced by a number of antiretroviral drugs including SQV-SGC. Approximately 12% of patients in this study had grade 0 to 1 shift of hyponatremia (130 - 135 mEq/L), and 1% with grade 0 to 2 shift (123 - 129 mEq/L). Therefore, patients on SQV-SGC should be monitored for hydration status and electrolyte balance.

8.2.10.4.4.2. Marked Laboratory Abnormalities

The sponsor defined marked laboratory abnormality as either a shift from grade 0 on day 1, to grade 3 or 4, or from grade 1 on day 1 to grade 4 during the study period. The sponsor's analysis dismissed a number of these abnormal laboratory data as artifacts since they occurred only in single isolated instances with no associated clinical adverse events.

The sponsor's tabulation of marked abnormal laboratory data is presented in Table 8.2.10.4.4.2.A.

Table 8.2.10.4.4.2.A. Summary of Marked Laboratory Abnormalities

Analyte	Number of Patients with Marked Laboratory Abnormality (N = 442)	
	n	(%)
↑ AST (SGOT)	9	(2.0)
↑ ALT (SGPT)	13	(2.9)
↑ Creatine kinase	13	(2.9)
↑ Amylase	1	(0.2)
↑ Total bilirubin	5	(1.1)
↑ Glucose	3	(0.7)
↓ Glucose	24	(5.4)
↑ Potassium	7	(1.6)
↑ Sodium	1	(0.2)
↓ Neutrophils	2	(0.5)
↓ Platelets	1	(0.2)

(Source: NV15182)

Reviewer's Comments

1. A review of laboratory data showed that the majority of markedly abnormal laboratory results were not confirmed by resubmission of new specimens.

2. Administration of protease inhibitors has been associated with onset of hyperglycemia and/or diabetes mellitus. A review of clinical and laboratory data on patients with marked glucose elevations in this study is summarized as follows:

- Patient 16989/2383, a 61-year-old male with normal baseline glucose, had a single elevated glucose level of 302 mg/dL (grade 3) on study day 29. This occurred while the patient had recurrent PCP and was treated with pentamidine, a drug known to be associated with hyperglycemia.

- Patient 17163/2996, a 36-year-old female, had a history of poorly controlled insulin-dependent diabetes mellitus. Her blood glucose fluctuated widely from 20.1 mmol/L (grade 4 elevation) at baseline to 1.5 mmol/L (normal 3.3-6.4 mmol/L) on study day 88.

- Patient 17007/2507 was a 51-year-old female with history of diabetes mellitus. Her baseline glucose levels were normal. However, throughout the treatment period, she exhibited persistently elevated glucose levels ranging from 133-264 mg/dL (grade 1-3).

- Patient 17002/2530, a 48-year-old male with normal glucose baseline, had glucose of 300 mg/dL (grade 3) on study day 85, which subsequently decreased to 137 mg/dL (grade 1) on day 106, and became normal on day 169.

The last two cases may represent diabetes mellitus exacerbated or induced, respectively, by SQV-SGC.

3. The sponsor stated that most of the markedly elevated creatine kinase results were isolated abnormalities and resulted from excessive exercise on the part of patients prior to blood collection. These patients apparently did not exhibit clinically overt musculo-skeletal abnormalities, and subsequent creatine kinase measurements appeared to normalize. A review of CRS showed that 9 out of 13 patients (69.2%) with marked CK abnormalities were on concomitant ZDV treatment. Please see this reviewer's comment on creatine kinase abnormalities in section 8.2.10.4.4.1.

4. It appeared from an examination of laboratory data that in a number of cases, the abnormally low glucose levels were accompanied by abnormally high potassium levels. Since there were no repeated confirmatory tests with new specimens, it was not clear if the abnormal results were in fact due to laboratory artifacts; i.e., delayed separation of serum from the clotted specimen.

5. Hyperkalemia has been reported as one of the electrolyte perturbations seen in HIV infection. However, it should also be noted that isolated and abnormally high potassium levels in an otherwise asymptomatic patient is frequently due to a hemolyzed specimen.

6. Patient 17004/2207, a 47-year-old male, was taken off the study from treatment on day 105 due to insufficient therapeutic response. On day 115 he had an abnormally high sodium of 161 mEq/L (grade 3) and abnormally high chloride level of 128 mEq/L (normal 94-109 mEq/L) while other electrolytes were normal. There was no record of clinical adverse events. These unusually abnormal results might have been caused by specimen collection distal to an intravenous fluid line.

7. All five cases of abnormally high total bilirubin levels occurred in patients with significantly elevated transaminases. Four of these patients had documented concurrent acute or chronic viral hepatitis. Further examination of sponsor's data also revealed that of the 13 patients with marked elevation of ALT, 9 patients had either concurrent viral hepatitis or a history of viral hepatitis. Of the 9 patients with

marked elevation of AST, 6 patients had evidence of viral hepatitis as shown in Table 8.2.10.4.4.2.C.

Table 8.2.10.4.4.2.C. Marked Abnormal Laboratories Associated with Known Viral Hepatitis Infection

Patient ID	Viral Hepatitis Infection	Maximum Abnormal Laboratory Value		
		AST (U/L)	ALT (U/L)	T. Bilirubin (mg/dL)
16984/2444	A, acute	199	*387*	*3.8*
16984/2454	C, chronic	*253*	*449*	1.0
16998/2712	B, chronic	172	*310*	0.6
16999/2051	A, acute	*646*	*723*	*3.2*
16992/2465	C, chronic	*367*	*760*	1.6
16993/2272	B, acute	*1135*	*2195*	*4.7*
16998/2711	A, acute	*461*	*1051*	*4.7*
17163/3004	C, chronic	*398*	*598*	13*

* µmol/L (normal: 3-21 µmol/L)
- Grade 3 toxicity for AST/ALT defined by sponsor as 5.1-10X upper normal limit
- *Italic*: grade 3 or 4 toxicity values
(FDA analysis of NV15182)

8. The sponsor reported two cases of grade 4 decreases of neutrophils as follows:

- Patient 17004/2212, a 35-year-old male, had one isolated differential neutrophil count of 14% (grade 3) with a concomitant increase of lymphocyte count of 66% and monocyte count of 15%. His total white cell count was stable at 3.0x10^9/L. His white cell count returned to baseline subsequently without alteration of study drug regimen.

- Patient 17193/2863, a 28-year-old male, had one isolated neutrophil differential count of 26% (grade 3) with concomitant increase of lymphocyte differential count of 55% and mild thrombocytopenia of 125x10^9/L on day 29. He also had a mild transient decrease of total white cell count from a pre-existing baseline of moderate leukopenia. Subsequent values fluctuated between normal and grade 1 toxicity.

In this reviewer's opinion, the single episode of relative neutropenia in the first case was probably unrelated to treatment.

9. There was one case of grade 3 thrombocytopenia (16988/2425) resulting in discontinuation of treatment. Please see section 8.2.10.4.4.3 for additional details.

8.2.10.4.4.3. Laboratory Abnormalities Associated with Premature Discontinuation of Treatment

The sponsor reported that 4 patients withdrew from the study due to laboratory toxicity. These cases are listed below:

- Patient 16988/2425, a 54-year-old male, developed thrombocytopenia of $60x10^9$/L on study day 29, and $25x10^9$/L on day 57. He was taken off SQV treatment on day 70. On day 74, his platelet count increased to $55x10^9$/L and $145x10^9$/L on day 85 and subsequently returned to his baseline level.

- Patient 17187/2887, a 29-year-old male with otherwise unremarkable clinical history and concomitant medications, had SQV treatment discontinued on day 122 due to progressively elevated creatine kinase. His baseline creatine kinase was slightly elevated at 225 U/L and increased to 552 U/L on day 87, 1563 U/L on day 120, 3180 on day 136 and decreased to 2530 on day 142. There were no further follow-up data after that time point. He also had concurrent elevation of AST and ALT (grade 1 to 2).

- Patient 16992/2465, a 49-year-old man, had progressive elevation of ALT and AST beginning on treatment day 55, to maximum of 760 U/L (grade 4 toxicity) and 367 U/L (grade 3), respectively, on day 85. The AP, total bilirubin and GGT levels were also increased. SQV-SGC was withheld until the ALT and AST returned to normal range. Upon restarting SQV-SGC, the transaminases began to rise. Treatment was discontinued on day 125.

- Patient 17196/2733, a 47-year-old male, was administratively discontinued from SQV therapy on day 65 due to "abnormal laboratory tests." He was diagnosed with cholelithiasis on study day 4. His alkaline phosphatase increased on day 17, peaked at 435 U/L (grade 2) on day 44, and subsequently decreased to slightly above normal on day 86. The AST, and ALT also exhibited mild (grade 1) increase during this period.

Reviewer's Comments:

1. Patient 16988/2425 experienced marked thrombocytopenia The time course of event was consistent with a drug-related phenomenon. It should be noted that marked thrombocytopenia has previously been reported in about 1% of patients on SQV-HGC treatment (NV14256).

2. The time course of laboratory abnormalities for patient 16992/2465 also appeared to be consistent with a drug-induced hepatotoxicity.

3. In this study, two patients were prematurely discontinued due to biliary tract disorders. One patient (16985/2100) had pre-existing sclerosing cholangitis prior to the study as discussed under the adverse events section (see section 8.2.10.4.2.3). The other patient described in this section, 17196/2733, had laboratory evidence consistent with cholecystitis as a complication of pre-existing cholelithiasis. His reason for early withdrawal was listed as "laboratory toxicity." However, it appeared that the intercurrent illness (cholelithiasis) was the primary reason for premature discontinuation (see discussion in the 48-week Safety Update).

8.2.10.4.4.4. Overdosage Exposure

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

9.2.9.4.4.5. Additional Analyses and Explorations

The original protocol did not identify triglycerides as part of the laboratory safety tests. Therefore, most, if not all, patients in this study did not have screening and baseline levels. In the latter part of the study, many patients had lipid profile tests performed on scheduled follow-up laboratory studies. A *post hoc* examination of laboratory results by this reviewer identified a high prevalence of hypertriglyceridemia in the study patients. Non-fasting triglyceride results in 100 patients randomly selected from 26 study centers are summarized in Table 8.2.10.4.4.5. For this exploratory analysis, only patients with at least two elevated triglyceride measurements greater than 250 mg/dL at any time during the study were considered to have hypertriglyceridemia. The highest triglyceride level from each patient was graded for severity using the ACTG toxicity criteria.

Table 8.2.10.4.4.5. Prevalence and Severity of Hypertriglyceridemia

Severity[1]	Percentage of Patients (n = 100)
Grade 0 (normal) (<250 mg/dL)	54
No ACTG grade specified (250-400 mg/dL)	24
Grade 2: moderate (401-750 mg/dL)	16
Grade 3: severe (751-1250 mg/dL)	5
Grade 4: very severe (>1250 mg/dL)	1

[1] ACTG grading scale
(Source: FDA Reviewer's analysis of NV15182)

Overall, 46% of patients had triglycerides >250 mg/dL. Approximately 24% of patients had triglyceride levels between 250 and 400 mg/dL (ACTG grading scheme does not specify "grade 1" hypertriglyceridemia), 16% had grade 2 elevation (400 - 750 mg/dL), 5% had grade 3 (751 - 1200 mg/dL), and 1% had grade 4 (>1200 mg/dL). It is of note that in cases where marked hypertriglyceridemia (grade 3 or 4 levels) were present, there was no concomitant hypercholesterolemia.

The prevalence of hypertriglyceridemia could be postulated to be a physiologic variation of a fed state, a pre-existing high prevalence of hypertriglyceridemia among the study patients, a potential drug effect, or a combination of these etiologies.

The sponsor stated that patients were encouraged to take SQV-SGC with "a meal or substantial snack." The sponsor also indicated that SQV package insert also encouraged a high-fat, high-calorie meal to maximize SQV plasma levels. In addition, approximately 15 g/day of , a mixture of saturated mono and diglycerides of caprylic and capric acid, were consumed by patients taking a clinical dose of SQV-SGC 1200 mg TID. And finally, specimens for laboratory studies were not collected after fasting. Therefore, the rise in triglyceride levels could have reflected physiologic variations due to postprandial state of patients at the time of blood drawing. While the validity of this explanation is acknowledged, it is worth noting that the reference ranges (approximately 40 - 250 mg/dL) for routine determinations of triglycerides in most clinical laboratories are based on random sampling and, hence, reflect the physiologic variability of triglycerides from fasting

to fed states. If it were true that hypertriglyceridemia was due to concomitant fatty food intake to increase SQV bioavaliability, the condition should be regarded as treatment related. Interestingly, results from a study of lipid metabolism[1] showed that after a high fat meal (110 g of fat, 46 g of protein, and 70 g of carbohydrate), postprandial plasma triglyceride concentrations elevated approximately 130 mg/dL in healthy control subjects (n = 10) to maximum levels of approximately 245 mg/dL after 4 hours.

Disturbances of lipid metabolism including hypocholesterolemia and hypertriglyceridemia have been reported in several prospective and retrospective studies to occur in HIV-infected patients[2]. The abnormalities were thought to be secondary to cytokine-mediated hepatic lipogenesis. While "hypocholesterolemia" (generally defined levels less than 150 mg/dL) is prevalent during the early stage of infection, hypertriglyceridemia frequently appears in patients with AIDS. In a controlled metabolic study on fasting plasma[3], triglycerides were shown to be 1.15 ± 0.122 mmol/L (101.9 ± 10.8 mg/dL), 1.24 ± 0.167 mmol/L (109.8 ± 14.8 mg/dL) and 2.29 ± 0.281 mmol/L (202.8 ± 24.9 mg/dL) in healthy control subjects (n = 16), HIV-positive patients (n = 14), and patients with AIDS (n = 15), respectively. The results of this study showed that although elevated serum triglycerides were seen in patients with AIDS, these increased levels were substantially lower than the ACTG grade 2 toxicity level (400 - 750 mg/dL).

A recent review of spontaneous post-marketing reports revealed several cases of markedly elevated triglycerides (up to 9000 mg/dL) accompanied by hypercholesterolemia and positive dechallenges in patients taking SQV-HGC. In one case, the patient experienced acute pancreatitis with positive rechallenge. During the second episode of pancreatitis, admission triglyceride level was 9.9 mmol/L

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[1]Cooper MB, Tan KCB, Hales CN, and Betteridge DJ. Postprandial lipid metabolism and cell function in non-insulin-dependent diabetes mellitus after a mixed meal with a high fat content. Diabet Med 1996, 13(9): 816-817

[2] Zangerle R, Sarclatti M, Gallati H, et al. Decreased plasma concentrations of HDL cholesterol in HIV-infected individuals are associated with immune activation. J Acquired Immune Defic Syndrome 1994, 7(11): 1149-1156

[3] Grunfeld C, Pang M, Doerrler W, et al. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J Clin Endocrinol Metab 1992 May, 74(5): 1045-1052

(reference range: 0.5 - 1.8 mmol/L). The patient subsequently developed pancreatorenal syndrome thought to be related to treatment. Significant hypertriglyceridemia has also been observed in patients on ritonavir therapy. Triglyceride levels of greater than 1,500 mg/dL were documented in approximately 1-2% of treatment naive patients (study 245) and 8-10% of advanced patients (study 247) on ritonavir therapy. Pancreatorenal syndrome has also been reported in one patient on ritonavir combination therapy[4] whose triglyceride level on admission was 20.9 mmol/L.

In summary, moderate to marked hypertriglyceridemia (>400 mg/dL) was present in approximately 22% of patients in this study. While the available data from this study are inconclusive in establishing a causal relationship between the test drug and hypertriglyceridemia, increased triglycerides have been associated with pancreatitis and clinical risks of cardiovascular diseases. It is prudent, therefore, that patients taking SQV-SGC, as well as other protease inhibitors, should have triglyceride levels monitored on a regular basis to allow timely intervention if clinically indicated.

Reviewer's Additional Comments

1. Upon FDA request, the sponsor provided the following for triglyceride results from studies NV15107, NV15182 and NV15355:

- In study NV15107, 24% of patients on SQV-SGC 1200 mg TID arm had grade 2 elevation of triglycerides, 14% had grade 3, and 4% had grade 4.

- In study NV15182 (48-week data), 20.1% of patients had grade 2 elevation of triglycerides, 4.1% had grade 3, and 1.3% had grade 4.

- In study NV15355, after 16 weeks of treatment, one patients (1.4%) on SQV-HGC arm had grade 0 to 2 shift of triglycerides compared to 9 patients (10%) on SQV-SGC arm with similar elevation. In addition, one patient on SQV-HGC arm had grade 2 to 4 shift of triglycerides.

The sponsor attributed the increased triglycerides in these patients to samples obtained during non-fasting state.

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[4] Stricker R, Man K, Bouvier D, et al. Pancreatorenal syndrome associated with combination antiretroviral therapy in HIV infection. Lancet 1997 June; 349: 1745-1746

2. Patient 16989/2381 developed acute pancreatitis on day 214 of treatment. His triglycerides were persistently elevated (between 629 to 1482 mg/mL) before the event. He was discontinued from the study after this episode. A follow-up triglyceride level was within normal limits.

8.2.10.5. Efficacy Outcomes

The sponsor provided descriptive summaries of two efficacy parameters, HIV RNA level and CD4 cell count, in terms of change from baseline and area under the curve (AUC) to assess treatment effect over time. Data for each parameter were presented in summary tables to include mean, median, standard deviation, minimum, maximum, interquartile range and number of observations. The median changes from baseline of HIV RNA and CD4 cell count were also plotted for 24 weeks of treatment.

8.2.10.5.1. HIV RNA Level

8.2.10.5.1.1. Baseline HIV RNA Distribution

The mean and median baseline HIV RNA levels were 4.14 and 4.25 $\log_{10}$ copies/mL, respectively, and the baseline interquartile range was 3.58 to 4.78 $\log_{10}$ copies/mL. Of 441 patients with recorded baseline HIV RNA, 30 patients (6.8%) had baseline HIV RNA below the limit of quantification (<400 copies/mL). The baseline HIV RNA data are summarized in Table 11, section 8.2.10.3.

8.2.10.5.1.2. HIV RNA Profile During Treatment Period

According to the sponsor, the reduction of $\log_{10}$ HIV RNA levels from baseline was skewed; therefore, emphasis was placed on the median and interquartile range. HIV RNA changes are summarized in Table 8.2.10.5.1.2.A.

At week 16, there were 386 patients with evaluable HIV RNA assessment. The number dropped significantly to 284 evaluable patients (26.4% loss) at week 24 due to withdrawals and/or lack of viral load data. Therefore, the comparison of data at these two time points could not be made with confidence.

The maximum viral suppression was achieved between week 8 and week 24, with the median change occurring at week 16 of treatment. At week 24, 82% of patients had a decrease in HIV RNA level, 14.8% had an increase, and 3.2% had no net change. The median maximal change was -1.21 $\log_{10}$ copies/mL

(interquartile -1.87 to -0.48 log_{10} copies/mL). The proportions of patients with HIV RNA below the limit of detection (<400 copies/mL) were 35.5% at week 4, and 42.6% at week 24 (Table 8.2.10.5.1.2.B). The area-under-the-curve (AUC) analysis up to week 24 shows a median of -0.62 log_{10} copies/mL and interquartile range of -1.25 to -0.11 copies/mL.

Table 8.2.10.5.1.2.A. Summary of HIV-RNA Change from Baseline (log_{10} copies/mL)

	Week 4	Week 8	Week 16	Week 24
N	409	406	386	284
Mean	-0.88	-0.84	-0.73	-0.86
Standard deviation	0.85	0.98	1.01	0.96
Minimum	-3.22	-3.42	-3.39	-3.42
Maximum	1.86	1.90	2.63	2.96
Median	-0.92	-0.78	-0.63	-0.83
Interquartile range				

(Source: NV15182)

Table 8.2.10.5.1.2.B. Summary of Proportion of Patients Below Limit of Detection

	Baseline	Week 4	Week 8	Week 16	Week 24
Percentage of patients	6.8%	35.5%	42.1%	40.2%	42.6%

(Source: NV15182)

Reviewer's Comments

1. The sponsor stated that the median changes from baseline of HIV RNA of the study population were negative (below baseline) at all visits from week 4 to week 24.

2. The efficacy results showed a median maximum HIV RNA decrease of -1.2 log_{10} copies/mL at week 16. In addition, approximately 43% of patients had HIV RNA levels below the limit of detection at week 24. The lack of higher viral suppression may have been related to the fact that the majority of patients (95.9%) were antiretroviral treatment experienced (see section 8.2.10.5.3.1).

8.2.10.5.2. CD4 Cell Count

8.2.10.5.2.1. Baseline CD4 Cell Count Distribution

According to the sponsor, the mean and median baseline CD4 cell counts were 221 cells/mm^3 and 201 cells/mm^3, respectively. The interquartile range was 91 to 345 cells/mm^3. Baseline CD4 cell count data are summarized in Table 8.2.10.3.C, section 8.2.10.3.

8.2.10.5.2.2. CD4 Cell Count Profile During Treatment Period

Changes from baseline of CD4 cell count are presented in Table 8.2.10.5.2.2.A. According to the sponsor, CD4 changes were skewed, hence, median and interquartile range were favored in the interpretation of CD4 cell count data. A large number of patients either withdrew from study or did not have CD4 cell count assessments performed at week 24. Therefore, the slight increase of CD4 cell count between week 16 and week 24 may not be meaningful. At week 24, 83.9% of patients had an increase in CD4 cell count, 15.8% had a decrease, and 1 patient had no net change. The maximal increase of CD4 cells occurred after week 12 of treatment with a median change of 99.8 cells/mm^3.

Table 8.2.10.5.2.2. Summary of CD4 Cell Count Change from Baseline (cells/mm^3)

	Week 4	Week 8	Week 12	Week 16	Week 24
N	417	398	370	388	310
Mean	32.7	45.5	65.9	59.8	79.7
Standard deviation	80.0	82.5	94.0	91.6	99.3
Minimum	-282.0	-274.5	-360.0	-328.0	-404.0
Maximum	372.0	398.0	470.0	506.5	566.0
Median	24.5	36.8	57.0	53.0	66.0
Interquartile range					

(Source: NV15182)

Reviewer's Comment

The sponsor observed that the median change from baseline of CD4 was positive at all visits (from week 4 to week 24).

8.2.10.5.3. Subgroup Analysis

The original protocol specified subgroup analysis based on CD4 stratification (<100 cells/mm^3, 101-250 cells/mm^3, and >250 cells/mm^3), and protease inhibitor treatment history, naive versus experienced. The sponsor subsequently added plans for other exploratory subgroup analyses (HIV RNA levels at screening, history of antiretroviral treatment, and history of previous SQV treatment) prior to the 24-week data analysis.

8.2.10.5.3.1. HIV RNA Results

Table 8.2.10.5.3.1 summarizes the sponsor's subgroup analysis of HIV-RNA results. The data did not show obvious distinctions between the three CD4 strata with regard to the median change from the baseline of HIV RNA. Patients with CD4 >250 cells/mm^3 appeared to have the lowest maximal viral suppression. Nevertheless, a higher proportion of them had viral load below the detection level at week 24. The maximum suppression occurred at week 8 for those with lower CD4 cell counts and those who had prior protease inhibitor treatment, whereas those with higher CD4 counts and those who were naive to protease inhibitors had maximal changes at week 16. Protease-naive patients appeared to have greater suppression of HIV RNA, and a higher proportion of them had HIV RNA levels below detection limit than those who were protease-inhibitor experienced.

Table 8.2.10.5.3.1. Summary of Subgroup Analysis of HIV RNA results (log_{10} copies/mL)

Subgroup	Week 24 Change from Baseline			Maximum Change from Baseline		
	n	Median	% BLQ*	n	Median	Median week
Safety population	284	-0.83	42.6	431	-1.21	16
CD4<100 cells/mm3	86	-0.68	24.4	122	-1.31	8
101<CD4<250 cells/mm3	91	-0.87	39.6	141	-1.29	8
CD4>250 cells/mm3	107	-0.87	59.8	168	-1.01	16
Protease-inhibitor naive	227	-0.95	46.3	353	-1.29	16
Protease-inhibitor experienced	57	-0.46	28.1	78	-0.74	8

*BLQ: Below Limit of Quantification (<400 log_{10} copies/mL)
(Source: NV15182)

8.2.10.5.3.2. CD4 Results

Table 8.2.10.5.3.2 summarizes the sponsor's subgroup analyses of CD4 cell count results. The baseline CD4 values as stratified did not appear to influence the change from the baseline of CD4 cell count after 24 weeks. Patients who were naive to protease inhibitor treatment had a slightly higher baseline CD4 cell count than the protease-inhibitor experienced group. These patients were observed to have higher increases in CD4 cell count at week 24. For both groups, the maximal CD4 cell count increase occurred at week 12.

Table 8.2.10.5.3.2. Summary of Subgroup Analysis of CD4 Cell Count Results (cells/mm^3)

Subgroup	Week 24 Change from Baseline		Maximum Median Change from Baseline		
	n	Median	n	Median	Median week
Safety population	310	66.0	434	99.8	12
CD4≤100 cells/mm^3	93	63.0	122	79.0	14
101≤CD4≤250 cells/mm^3	97	61.0	142	94.0	12
CD4>250 cells/mm^3	120	76.8	170	131.0	12
Protease-inhibitor naive	249	72.5	356	103.0	12
Protease-inhibitor experienced	61	48.0	78	81.8	12

(Source: NV15182)

8.2.10.5.3.3. Exploratory Subgroup Analysis

Other exploratory subgroup analyses showed that, at week 24, a higher percentage of patients (60.1%) with baseline HIV RNA level <20,000 copies/mm^3 had HIV RNA suppression below the limit of detection of the assay compared to those whose baseline HIV RNA levels were >20,000 copies/mm^3 (23.5%). The median changes from baseline in CD4 cell counts were not appreciably different among the two groups. SQV-naive patients had better viral suppression (-0.92 $\log_{10}$ copies/mL HIV RNA) than those who were SQV-experienced prior to starting therapy (-0.48 $\log_{10}$ copies/mL HIV RNA). Likewise, patients who started with one or two new nucleosides or non-nucleoside reverse transcriptase inhibitors had better viral suppression and CD4 cell count improvement. The results of sponsor's analyses are summarized in Tables 8.2.10.5.3.3.A and 8.2.10.5.3.3.B.

Table 8.2.10.5.3.3.A. Summary of Subgroups Exploratory Analysis of HIV RNA Results (log_{10} copies/mL)

Subgroup	Week 24 Change from Baseline			Maximum Median Change from Baseline		
	n	Median	% BLD*	n	Median	Median week
Safety population	284	-0.83	42.6	431	-1.21	16
RNA<20,000 copies/mL	148	-0.60	60.1	225	-0.90	16
RNA≥20,000 copies/mL	136	-1.06	23.5	206	-1.61	8
Antiretroviral treatment						
- naive	8	-1.88	75.0	17	-1.86	16
- Non-naive	276	-0.75	41.7	414	-1.17	16
SQV naive	234	-0.92	46.2	361	-1.28	16
SQV non-naive	50	-0.48	26.0	70	-0.67	8
No new RTI	245	-0.67	42.4	379	-1.13	8
≥1 new RTI	39	-1.10	43.6	52	-1.61	16
≥2 new RTI	18	-1.06	50.0	23	-1.58	16

(Source: NV15182)

Table 8.2.10.5.3.3.B. Summary of Subgroup Exploratory Analysis of CD4 Cell Count Results (cells/mm^3)

Subgroup	Week 24 Change from Baseline		Maximum Median Change from Baseline		
	n	Median	n	Median	Median week
Safety population	310	66.0	434	99.8	12
RNA<20,000 copies/mL	164	59.8	227	102.5	12
RNA≥20,000 copies/mL	146	76.0	207	97.5	12
Antiretroviral treatment					
- naive	9	207.0	17	190.5	12
- Non-naive	301	63.0	417	97.5	12
SQV naive	257	72.5	364	103.0	12
SQV non-naive	53	48.0	70	81.8	12
No new RTI	271	62.5	382	96.5	12
≥1 new RTI	39	97.5	52	146.0	12
≥2 new RTIs	18	131.5	23	174.0	12

(Source: NV15182)

Reviewer's Comment

The sponsor was able to show that treatment-naive patients, patients with HIV RNA < 20,000 copies/mL, and patients starting the study with new RTI(s) had better treatment responses in terms of viral suppression and improved CD4 cell counts. However, the data also identified a small number of SQV-HGC experienced patients who showed relatively poor responses with SQV-SGC containing regimens. ACTG-333 study also appeared to confirm these results for patients with prior SQV-HGC treatment.

8.2.10. Conclusions

This open-label trial was conducted primarily to collect safety data on SQV-SGC in combination with other antiretroviral drugs. Since the study was not a controlled trial with comparison arm, the safety data as well as efficacy results from this trial could not be evaluated with respect to other treatments. A total of 442 patients were enrolled in the trial, of which, 382 (86.4%) completed 24 weeks of treatment. Patients were exposed to SQV-SGC for a median of 196 days.

During the study period, there were 3 deaths from conditions associated with advanced HIV-infection. Although 91.2% of patients experienced one or more clinical adverse events, the safety data appeared to support the conclusion that SQV-SGC was safe and relatively well tolerated by a majority of patients in the trial. Only 6.1% of patients withdrew from the study due to adverse events, and 0.7% due to laboratory abnormalities. There were no unexpected treatment-emergent adverse events after 24 weeks of therapy compared to the experience with the SQV-HGC formulation. The most common adverse events, excluding those unrelated to treatment, were diarrhea (34.4%), nausea (21.7%), and dyspepsia (17.4%). Abdominal complaints ranging from discomfort to pain were noted in 23.1% of patients. Other notable adverse events were headache (11.5%), fatigue (10.6%), flatulence (9.3%), and vomiting (5.9%). The majority of adverse events were predominantly mild in intensity. These incidences of adverse events represented increases above those observed in trials with the SQV-HGC formulation.

Laboratory parameters showed evidence of hepatotoxicity (elevated ALT, AST), mostly mild to moderate (grade 1 or 2) levels, in approximately 20% of patients. Other significant laboratory abnormalities of grade 1 or 2 were asymptomatic elevation of CK (28.7%), hyperamylasemia (11.7%), hyperglycemia (31.5%), hypoglycemia (15.0%) and hyponatremia (10.7%). While these laboratory abnormalities have been reported to be prevalent in HIV-infected patients, the role

of SQV-SGC treatment in causing or exacerbating them is unknown.

The sponsor was also able to show that SQV-SGC in combination with other antiretroviral drugs produced a median maximum viral suppression of approximately -1.2 $\log_{10}$ copies/mL occurring at week 16, and a median maximum CD4 increase of 100 cells/mm^3 at week 13. By week 24, 42.6% of patients had viral load below the quantifiable level (<400 copies/mL). The lack of higher antiviral activity was partially due to patient selection; i.e., the majority of patients on this trial (95.9%) were antiretroviral treatment-experienced. Among the relatively small number of treatment-naive patients, the efficacy appeared to be more pronounced; 75% of these patients had HIV RNA falling below 400 copies/mL at week 24. Subgroup analyses also appeared to support the observations that better viral suppression and CD4 cell count improvement were achieved in patients with high baseline CD4 cell counts, and those who started SQV-SGC in combination with new reverse transcriptase inhibitors.

8.3. Protocol NV15355

8.3.1. Protocol Title

A randomized, parallel arm, comparative, open label, multicenter study of the activity and safety of two formulations of saquinavir in combination with two nucleosides antiretroviral drugs in treatment naive patients.

8.3.2. Objectives

The primary objectives of this study was to evaluate the antiviral activity and safety of SQV-HGC and SQV-SGC in combination with other antiretroviral drugs in treatment-naive patients for a study period of 48 weeks.

8.3.3. Study Design

The study was to be conducted at up to 25 centers in the U.S. and Canada. A total of 140 HIV-infected patients was to be enrolled to provide at least 100 evaluable patients. The patients were to be equally randomized into two treatment arms as follows:

A.	SQV-HGC 600 mg po TID + 2 RTIs	($n_1 = 70$)
B.	SQV-SGC 1200 mg po TID + 2RTIs	($n_2 = 70$)

The study was designed to have a 16-week randomized treatment period followed by an extension phase lasting up to 48 weeks during which patients would be allowed to switch to the SQV formulation of choice. Preliminary safety and efficacy analyses were to be conducted at week 16 for this NDA submission.

Patients were to be stratified based on HIV RNA at baseline into two groups, i.e., ≥20,000 copies/mL (>25% of patients) and <20,000 copies/mL (>25% of patients).

Reviewer's Comment

The sponsor enrolled 179 patients, of these, 171 took medication. Eighty one patients were randomized into treatment arm A, and 90 to arm B. A total of 24 patients prematurely withdrew from the study leaving 147 in the study by week 16.

8.3.4. Patient Population

The study was to be conducted in treatment-naive male or female HIV-infected patients. Treatment naivety was defined by the sponsor as having had no history of protease inhibitor treatment, ≤4 weeks of treatment with any licenced nucleoside antiretroviral drug, and no antiretroviral treatment 28 days prior to screening.

The eligibility criteria also included patients, 13 years or older, with HIV RNA ≥5000 copies/mL, no history of transfusion dependency, hemoglobin ≥8.0 g/dL, absolute neutrophil count >750/mm^3, platelet count ≥50,000/mm^3, transaminases <2.5x the upper normal limit, total bilirubin <1.5x upper normal limit, and creatinine clearance ≥75mL/min.

Patients with malabsorption, inability to maintain adequate oral intake, grade III or more laboratory or clinical abnormalities (except for exercise induced elevated creatine kinase), an active opportunistic infection, serious AIDS-defining event, chronic diarrhea, or malignancy were to be excluded. Inadequate contraception in female patients would be a reason for exclusion.

Patients with significant liver dysfunction, history of hemophilia or diabetes were to be closely monitored for underlying diseases.

Reviewer's Comment

Treatment-naive patients as defined by the sponsor is probably more accurately described as "minimally treated" patients.

8.3.5. Concomitant Medication

Patients were allowed to combine SQV-SGC with licensed nucleoside antiretroviral drugs. Other protease inhibitors were not to be concomitantly taken. Investigational immunomodulatory medications were not allowed during the 16-week randomized treatment period.

Since SQV metabolism has been shown to be mediated by CYP3A4 isoenzyme of cytochrome P_{450}, the sponsor placed emphasis on prohibiting or restricting the use of drugs which could potentially interact with SQV. The list of these drugs was similar to those of other studies reviewed previously.

8.3.6. Treatment Compliance

The sponsor did not include a plan to assess patients for treatment compliance or accountability of drug supplies.

The sponsor planned to include periodic drug screens to detect prohibited medications during the study.

8.3.7. Endpoints

8.3.7.1. Activity Endpoints

The primary activity parameter in this study was the change from baseline in HIV RNA averaged over 16 weeks. Secondary parameters were time to virologic relapse; proportions of patients with virologic response, relapse, failures, and viral load below the detection level; CD4, CD8, CD4%, CD8%, and absolute lymphocyte counts.

Virologic response was defined as either achieving an unquantifiable level of virus during the randomized treatment period, or a decrease greater than 2.0 $\log_{10}$ RNA copies/mL from baseline to any single assessment. Virologic relapse was defined as either two consecutive measurements greater than 0.5 log10 HIV RNA copies/mL above the level of quantification for those initially achieving an unquantifiable level of virus, or two consecutive measurements greater than 0.5

log_{10} copies/mL above the level of virologic response. Virologic failure was defined as either virologic non-response, or patients who have experienced virologic relapse.

Time to virologic relapse was to be calculated as the difference in days between the date of virologic response (the first visit at which a virologic response was to be observed) and the date of virologic relapse (the first visit of the two consecutive visits specified in the definition of virologic relapse above).

Reviewer's Comment

At the time this protocol was designed, there were no working definitions of virologic response or failure. The HIV RNA changes from the baseline over time were the primary method for evaluating virologic response.

8.3.7.2. Safety Endpoints

Safety parameters included monitoring of adverse events and laboratory safety tests during treatment.

8.3.8. Premature Discontinuation of Treatment

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

In addition, patients could be permanently discontinued from the study for reasons of toxicity, pregnancy, or malignancy requiring systemic treatment.

8.3.9. Analysis and Statistical Plans

8.3.9.1. Activity Analysis

The intent-to-treat (ITT) population was defined as all randomized patients who have received at least one dose of study drug. However, the sponsor planned to exclude those patients with missing baseline values or any values during treatment from the analysis of that parameter. A standard population was defined as the total number of randomized patients after excluding those with less than 75% compliance with study drug, those with missed doses, and those withdrawn prematurely from the study.

The baseline for the randomized treatment period was defined as the mean of two consecutive determinations before randomization (the first taken between day -23 and -8 and the second on day 1).

The sponsor stated that emphasis would be placed on the intent-to-treat analysis of efficacy after all patients have completed the 16-week randomized treatment period. A standard analysis of efficacy would be preformed to assess the influence of protocol violators on the treatment difference. Further exploratory analyses would be performed at the end of the study; i.e., after 48 weeks of treatment.

The primary comparison of HIV RNA changes between the two treatment groups would be performed by analysis of covariance to include region, treatment, and HIV RNA stratification (≥20,000 copies/mL and <20,000 copies/mL) at entry. In addition, CD4 cell counts at baseline as covariates would be included in the comparison tests between the two treatment groups.

Descriptive analyses of activity data up to week 16 (changes from baseline, AUCMB, DAVG of $\log_{10}$ HIV RNA, CD4, CD8 and absolute lymphocyte counts would be presented. No statistical tests were planned for CD4 , CD8, and absolute lymphocyte count parameters.

Secondary analyses using Kaplan-Meier estimate and two-sided log-rank test at an α-level of 5% would be used for the time to virologic relapse. Exploratory analyses on the proportion of patients with viral load below detection level, proportion of virologic response, failure and relapse would be performed using a two-sided χ^2 test at α-level of 5%.

8.3.9.2. Safety Analysis

Adverse events were to be classified by the ACTG grading system; i.e., grade 1 (mild), grade 2 (moderate), grade 3 (severe), and grade 4 (life-threatening). In addition, adverse events not defined by the ACTG grading system would be classified as mild (easily tolerated on continuation of treatment), moderate (sufficiently discomforting to interfere with usual activity), severe (incapacitating to prevent work or daily activity), and potentially life-threatening. Grade 1 adverse events or laboratory toxicities would not prevent a patient from continuing therapy. Decisions to continue with treatment in grade 2 cases would be left to the discretion of investigator. All grade 3 and 4 cases would result in temporary cessation of treatment until the toxicity has returned to at least grade 2. All grade 4 cases attributable to SQV would result in permanent discontinuation of treatment. The relationship of adverse events to treatment would be similarly

assessed as presented in previous protocols (see section 8.1.8).

Serious adverse event, overdose, death, or pregnancy were to be reported.

Laboratory safety tests were to be collected at intervals and analyzed by a central laboratory for the following parameters:

- Hematology: hemoglobin, hematocrit, white cell count with differential, and platelet count.

- Chemistry: electrolytes, random glucose, creatinine, albumin, calcium, phosphorus, CK, AST, ALT, GGT, AP, bilirubin (total, conjugated, unconjugated), triglyceride, cholesterol, LDL- and HDL-cholesterol.

Urinalysis: blood, protein, glucose, pH, and microscopic analysis.

All randomized patients who have received at least one dose of study drug and a safety follow-up were to be included in the safety analysis.

The sponsor included a schedule of assessments for the randomized period as shown in Table 8.3.9.2.

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Table. 8.3.9.2. Schedule of Assessments

	Screen	Baseline	Treatment Period												
	Days		Weeks												
	-28 to -19	-23 to -8	1[a]	4	8	12	16	20 (f)	24	28 (f)	32	40	48	Every 12 weeks	Last visit	Off-therapy[g]
Informed consent	x															
History & physical exam	x															
Weight	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum/urine β-HCG[b]		x														
Chest X-ray	x															
EKG[c]	x															
Hepatitis screen (B and C)	x															
CD4, CD4%, CD8, CD8%, lymphocyte count	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
HIV RNA (PCR)[d,e]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology/chemistry	x			x	x	x	x	x	x	x	x	x	x	x	x	
Urinalysis	x															
Plasma for genotype			x	x	x	x	x	x	x	x	x	x	x	x	x	
PBMC preservation			x				x		x				x	x	x	
Symptom-directed physical examination			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events				x	x	x	x	x	x	x	x	x	x	x	x	x

[a] Immediately before, but not on the same day as the first dose of study drug.
[b] For female patients, with 14 days of start of test drug; repeat for secondary amenorrhea during study.
[c] For patients with history of heart disease, IV drug use, or ≥45 years.
[d] Screen determinations must be at least 5 days before the firs baseline determination. Baseline and other determinations must be at least 14 days apart.
[e] A portion of stored plasma may be used for quality assurance purposes; to screen for medications prohibited by the protocol.
[f] Only for patients rolling over from hard gel to soft gel.
[g] If study treatment has been permanently discontinued, 4 weeks after last dose of study treatment.
(Source: NV15355)

8.3.10. Results

8.3.10.1. Patient Disposition

The study enrolled 179 patients, of these, 171 took medication. Eighty-one patients were randomized to SQV-HGC treatment arm (SQV-HGC, 600 mg TID + 2 RTIs), and 90 to SQV-SGC arm (SQV-SGC, 1200 mg TID + 2 RTIs). A total of 24 patients prematurely withdrew from the study by the cut-off date for 16-week analysis. The disposition of patients, according to the sponsor's and FDA reviewer's tabulations, is summarized in Table 8.3.10.1.

Table 8.3.10.1. Disposition of Patients

Patient Disposition	SQV-HGC Treatment Arm	SQV-SGC Treatment Arm
Randomized	86	93
Evaluable	81	90
Premature withdrawals		
- adverse event	1	9
- refused treatment/noncompliance/ withdrew consent	1	5
- lost to follow-up	5	1
- protocol violation	-	1
- administrative reason	-	1

(Source: NV15355)

Reviewer's Comments

1. More patients from the SQV-SGC treatment arm (n = 9) prematurely withdrew from treatment due to adverse events than those from the SQV-HGC arm (n = 1).

2. Additional information was requested from the sponsor regarding the premature withdrawal cases. Upon reviewing the reports, this reviewer agreed with the sponsor's overall classification of prematurely discontinued cases as shown in Table 8.3.10.1 above.

3. It was of note from the CRF review that patient 18013/7382 (SQV-SGC arm), a 43-year-old woman, was discontinued from the study since she was unable to swallow SQV-SGC pills due to their size, even with repeated attempts.

8.3.10.2. Patients with Protocol Deviation

One patient from the SQV-SGC treatment arm was discontinued due to the use of ritonavir, a prohibited medication.

8.3.10.3. Demographic Data

The sponsor's summary of demographic data of the study population is presented in Table 8.3.10.3.A

Table 8.3.10.3.A. Summary of Demographic Data

Demography	SQV-HGC Treatment Arm		SQV-SGC Treatment Arm	
	n	(%)	n	(%)
SEX				
Male	74	(91)	83	(92)
Female	7	(9)	7	(8)
RACE				
White	56	(69)	61	(68)
Black	17	(21)	16	(18)
Hispanic	6	(7)	12	(13)
Oriental	0		0	
Other	2	(2)	1	(1)
AGE				
Mean	35.5		38.3	
Range	18 - 63		18 - 60	
HEIGHT (cm)				
Mean	175.0		175.2	
Range	110 - 196		157 - 195	
WEIGHT (Kg)				
Mean	80.3		78.3	
Range	49 - 138		52 - 128	

(Source: NV15355)

The baseline characteristics of patients in terms of CD4 cell count and HIV RNA viral load are summarized in Table 8.3.10.3.B. In the SQV-HGC group, the mean CD4 cell count at baseline was 408 cells/mm^3 and the mean HIV RNA level was 4.8 log_{10} copies/mL. The SQV-SGC group had a slightly higher mean CD4 cell count at baseline of 447.5 cells/mL and similar mean HIV RNA level of 4.8 log_{10} copies/mL.

Table 8.3.10.3.B. Summary of Baseline CD4 and HIV RNA

Baseline Values	CD4 (cells/mL)		HIV RNA (log_{10} copies/mm^3)	
	SQV-HGC Treatment Arm	SQV-SGC Treatment Arm	SQV-HGC Treatment Arm	SQV-SGC Treatment Arm
N	81	89	81	90
Mean	408.0	447.5	4.8	4.8
Standard deviation	222.4	244.1	0.5	0.5
Minimum	3.5	6.5	3.5	3.6
Minimum	993.5	1303.5	5.9	5.9
Median	401.0	446.5	4.8	4.8
Interquartile range				

(Source: NV15355)

Reviewer's Comment

1. The patient populations of both treatment groups were comparable with regard to age, sex, race, as well as baseline virological and immunological status. The profile of study patients also appeared to better reflect the gender and ethnicity of HIV-infected patient population in the U.S. than what was seen in study NV15182.

2. No pediatric patients were enrolled in this study.

3. The study patients, overall, had relatively high CD4 cell counts and at the same time, relatively high HIV RNA levels.

8.3.10.4. Safety Outcomes

8.3.10.4.1. Drug Exposure

The extent of exposure to treatment is summarized in Table 8.3.10.4.1. It appeared that the majority of dropouts occurred in the first 4 weeks of study.

Table 8.3.10.4.1. Summary of Exposure to study Treatment

Treatment Duration (weeks)	SQV-HGC Treatment Arm	SQV-SGC Treatment Arm
4	81	90
8	78	81
12	76	76
16	75	75
>16	74	72

(Source: NV15355)

8.3.10.4.2. Adverse Events

8.3.10.4.2.1. Overview of Adverse Events

The sponsor presented safety data collected from the initial 16 weeks of the study. It appeared that a higher proportion of adverse events was reported in the SQV-SGC group than in the SQV-HGC group (70% versus 58%, respectively). Gastrointestinal adverse events; i.e., diarrhea, nausea, flatulence, dyspepsia, vomiting and abdominal complaints led the lists in both groups. Most of these events were of mild to moderate intensity. The frequency of dyspepsia, abdominal pain and vomiting were disproportionally higher in patients taking SQV-SGC 1200 mg. Headache and fatigue were also frequent complaints in both groups. Summaries of treatment-emergent adverse events occurring in 2% or more of study patients in the SQV-HGC group are presented in the next 2 Tables. Table 8.3.10.4.2.1.A summarizes treatment-related adverse events of at least moderate intensity for both treatment groups. Table 8.3.10.4.2.1.B lists treatment-related adverse events classified by intensity of the SQV-HGC treatment group. Table 8.3.10.4.2.1.C lists treatment-related adverse events classified by intensity of the SQV-SGC treatment group.

Table 8.3.10.4.2.1.A. Summary of Patients with Treatment-Emergent Adverse Events[1] of at least Moderate Intensity Occurring in ≥2% Patients

Body System/Disorder	SQV-HGC (N = 81)		SQV-SGC (N = 90)	
	n	(%)	n	(%)
Body as a whole				
Headache	4	(4.9)	8	(8.9)
Fatigue	5	(6.2)	6	(6.7)
Abdominal discomfort	4	(4.9)	12	(13.3)
Abdominal pain	1	(1.2)	7	(7.8)
Gastrointestinal				
Nausea	11	(13.6)	16	(17.8)
Diarrhea	10	(12.3)	14	(15.6)
Flatulence	6	(7.4)	11	(12.2)
Dyspepsia	2	(2.5)	9	(10.0)
Vomiting	1	(1.2)	4	(4.4)
Constipation	-		3	(3.3)
Psychiatric				
Insomnia	1	(1.2)	5	(5.6)
Anxiety	2	(2.5)	2	(2.2)
Libido disorder	-		2	(2.2)
Musculoskeletal				
Pain (NOS)	3	(3.7)	3	(3.3)
Nervous				
Taste alteration	1	(1.2)	4	(4.4)
Dermatological				
Rash	4	(4.9)	-	
Others				
Verruca	-		2	(2.2)

[1] Includes adverse events related to treatment, of unknown intensity and/or relationship to treatment.
(Source: FDA Reviewer's analysis of NV15355)

Table 8.3.10.4.2.1.B. Summary of Treatment-Emergent Adverse Events[1] Classified by Intensity Reported in ≥2% of Patients (SQV-HGC Group)

Body System/Disorder	Total (N = 81)		Mild		Moderate		Severe		Life-threatening		Unknown Intensity[2]
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
Body as a whole											
Fatigue	10	(12.3)	4	(4.9)	3	(3.7)	-		-		3
Headache	9	(11.1)	3	(3.7)	2	(2.5)	-		-		4
Abdominal discomfort	8	(9.9)	5	(6.2)	2	(2.5)	-		-		1
Abdominal pain	2	(2.5)	2	(2.5)	-		-		-		-
Decreased appetite	2	(2.5)	2	(2.5)	-		-		-		-
Gastrointestinal											
Diarrhea	24	(29.6)	15	(18.5)	7	(8.6)	2	(2.5)	-		2
Nausea	20	(24.7)	12	(14.8)	5	(6.2)	-		-		3
Flatulence	9	(11.1)	3	(3.7)	2	(2.5)	-		-		4
Dyspepsia	8	(9.9)	6	(7.4)	1	(1.2)	1	(1.2)	-		1
Vomiting	2	(2.5)	1	(1.2)	-		-		-		-
Musculoskeletal											
Myalgia	2	(2.5)	2	(2.5)	-		-		-		-
Pain (NOS)	2	(2.5)	1	(1.2)	-		-		-		1
Nervous											
Paresthesia	2	(2.5)	2	(2.5)	-		-		-		-
Taste alteration	2	(2.5)	1	(1.2)	-		-		-		1
Syncope	2	(2.5)	1	(1.2)	1	(1.2)	-		-		-
Bleeding and clotting											
Dermal bleeding	2	(2.5)	1	(1.2)	1	(1.2)	-		-		-

[1] Excludes adverse events unrelated to trial treatment.
[2] Unspecified by investigators.
NOS: Not Otherwise Specified
(Source: FDA Reviewer's analysis of NV15355)

Table 8.3.10.4.2.1.C. Summary of Treatment-Emergent Adverse Events[1] Classified by Intensity Reported in ≥2% of Patients (SQV-SGC Group)

Body System/Disorder	Total (N = 90)		Mild		Moderate		Severe		Life-threatening		Unknown Intensity[2]
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n
Body as a whole											
Headache	14	(15.6)	6	(6.7)	4	(4.4)	1	(1.1)	-		3
Fatigue	13	(14.4)	4	(4.4)	2	(2.2)	-		-		6
Abdominal discomfort	9	(10.0)	2	(2.2)	3	(3.3)	-		-		4
Abdominal pain	7	(7.8)	1	(1.1)	4	(4.4)	-		-		2
Decreased appetite	4	(4.4)	3	(3.3)	-		-		-		1
Fever	4	(4.4)	3	(3.3)	-		-		-		1
Gastrointestinal											
Diarrhea	28	(31.1)	18	(20.0)	6	(6.7)	2	(2.2)	-		2
Nausea	28	(31.1)	17	(18.9)	7	(7.8)	1	(1.1)	-		3
Dyspepsia	16	(17.8)	11	(12.2)	1	(1.1)	-		-		4
Flatulence	12	(13.3)	4	(4.4)	2	(2.2)	-		-		6
Vomiting	8	(8.8)	3	(3.3)	4	(4.4)	1	(1.1)	-		
Constipation	4	(4.4)	3	(3.3)	-						1
Musculoskeletal											
Pain (NOS)	3	(3.3)	-		2	(2.2)	1	(1.1)	-		1
Myalgia	2	(2.2)	2	(2.2)	-		-		-		-
Nervous											
Taste alteration	6	(6.7)	2	(2.2)	3	(3.3)	1	(1.1)	-		-
Extremity numbness	2	(2.2)	2	(2.2)	-		-		-		-
Psychiatric											
Insomnia	3	(3.3)	-		-		-		-		3
Irritability	2	(2.2)	1	(1.1)	-		-		-		1
Dermatologic											
Rash	3	(3.3)	2	(2.2)	-		-		-		1
Others											
Dyspnea	2	(2.2)	1	(1.1)	-		-		-		1

[1] Excludes adverse events unrelated to trial treatment.
[2] Unspecified by investigators.
NOS: Not Otherwise Specified
(Source: FDA Reviewer's analysis of NV15355)

Reviewer's Comments

1. It should be emphasized that the safety data presented above represented those seen after a relatively short duration of drug exposure (16 weeks) and in a relatively small number of patients. Nevertheless, it is clear from the data that while patients on SQV-SGC treatment arm had a similar adverse event profile as those on SQV-HGC arm, a relatively higher number of adverse events were observed in these patients.

2. This reviewer generally agrees with the sponsor's analyses of adverse events as presented above. However, the following classifications have been modified in the Tables above by this reviewer since distinctions between them are not readily or clinically discernable:

- "Eructation," "gastroesophageal reflux" and "pyrosis" are frequent findings of "dyspepsia" and are classified as such.

- "Photosensitivity reaction" of the skin most commonly manifests itself as a nonspecific "rash" and is classified as such. "Eczema" is classified as "rash."

- "Malaise" and "fatigue" are classified as "fatigue."

- "Anorexia" and "decreased appetite" are classified as "decreased appetite."

8.3.10.4.2.2. Serious and Life-Threatening Adverse Events

According to the sponsor, 6 patients on the SQV-HGC arm experienced serious adverse events including stroke, meningitis, sweat gland disorder, cellulitis, spinal cord disorder, and a suicide attempt. The patient with meningitis was thought to have a life threatening condition. None of these events were thought to be related to treatment.

Eight patients on the SQV-SGC arm had serious adverse events, seven of which were considered unrelated to treatment; i.e., severe pulmonary disease, cardiac failure, severe pharyngitis, pneumonia, sinusitis, vascular disorder and myocardial ischemia. One patient had moderate abdominal pain thought to be possibly related to treatment.

Reviewer's Comment

The CRFs of these above cases were reviewed. This reviewer agreed with the sponsor's assessments.

8.3.10.4.2.3. Adverse Events Associated with Premature Discontinuation of Treatment

The sponsor reported that one patient on the SQV-HGC arm experienced moderate nausea and was prematurely withdrawn from the study. On the other hand, nine patients from the SQV-SGC arm were discontinued early due to adverse events. The most common adverse events in these patients were diarrhea, nausea and vomiting, and dyspepsia ranging from moderate to severe intensity. One patient had myocardial infarction and the event was thought to be unrelated to treatment.

Reviewer's Comment

Gastrointestinal disorders (diarrhea, nausea, vomiting, dyspepsia) have been shown to be the most common adverse events and resulted in about 8% of patients being prematurely withdrawn from the safety study (NV15182) after 48 week of treatment. These adverse events occurred more frequently in the SQV-SGC arm compared to the SQV-HGC arm (10.0% versus 1.2%, respectively). They also accounted for approximately half of the SQV-SGC premature discontinuations.

8.3.10.4.3. Death

The sponsor reported no deaths during the study period.

8.3.10.4.4. Laboratory Findings

8.3.10.4.4.1. Overview of Laboratory Abnormalities

The frequencies of low-grade (grade 0 to grade 1) laboratory shifts in patients from both SQV-HGC and SQV-SGC treatment arms appeared to have similar distributions as those seen in study NV15182. These results are summarized in Tables 8.3.10.4.4.1.A and B. Patients in both groups had mildly elevated ALT, AST, bilirubin and creatine kinase levels. A significant proportion of patients in the study had hyponatremia (9.5% in the SQV-HGC group, 14.6% in SQV-SGC). Less than 5% of patients in each arm had other electrolyte abnormalities or calcium and phosphate imbalances. A relatively higher number of patients had low-grade hypoglycemia in the SQV-SGC group (16.7%) versus 8.4% in the SQV-HGC group.

The frequencies of low-grade hyperglycemia were similar in both groups (15.9% in the SQV-HGC group; 18.2% in SQV-SGC). Data on triglycerides showed a disproportionally higher frequency of moderate shift of (grade 0 to 2) triglycerides in patients of the SQV-SGC arm (11.5%) than that of SQV-HGC arm (1.4%).

Table 8.3.10.4.4.1.A. Percentage of Patients with Abnormal Laboratory Shifts from Normal Baseline (SQV-HGC Group)

Analyte	Percentage of Patients			
	0 - 1	0 - 2	0 - 3	0 - 4
↑ Alkaline phosphatase	1.3	-	-	-
↑ AST (SGOT)	11.4	4.3	-	-
↑ ALT (SGPT)	13.1	6.6	-	-
↓ GGT	1.7	-	-	
↑ Total bilirubin	5.3	2.7	-	-
↑ Creatine kinase (CK)	29.0	3.2	-	-
Amylase	NP	NP	NP	NP
↑ Glucose	15.9	1.4	-	-
↓ Glucose	8.4	4.2	1.4	1.4
↑ Calcium	3.9	-	-	-
↓ Calcium	-	-	-	-
↓ Phosphate	5.3	-	-	-
↑ Creatinine	2.6	-	-	-
↑ Potassium	1.3	-	-	-
↓ Potassium	1.3	-	-	-
↑ Sodium	1.3	-	-	-
↓ Sodium	9.5	-	-	-
↑ Triglycerides	-	1.4	-	-
Cholesterol*	11.1	-	-	-
↓ Hemoglobin	-	1.3	-	-
↓ Neutrophil count	8.1	-	3.2	-
↓ Platelet count	1.4	-	-	-

* American Heart Association grading
(Source: FDA Analysis of NV15355)

Table 8.3.10.4.4.1.B. Percentage of Patients with Abnormal Laboratory Shifts from Normal Baseline (SQV-SGC Group)

Analyte	Percentage of Patients			
	0 - 1	0 - 2	0 - 3	0 - 4
↑ Alkaline phosphatase	3.6	1.2	-	-
↑ AST (SGOT)	7.8	1.3	-	-
↑ ALT (SGPT)	16.2	6.8	1.3	-
↓ GGT	15.7	2.9	1.4	1.4
↑ Total bilirubin	9.3	1.2	-	-
↑ Creatine kinase (CK)	14.9	3.0	1.5	-
Amylase	NP	NP	NP	NP
↑ Glucose	18.2	3.9	-	-
↓ Glucose	16.7	2.4	3.6	-
↑ Calcium	-	-	-	-
↓ Calcium	2.4	1.2	-	-
↓ Phosphate	3.7	-	-	-
↑ Creatinine	1.2	-	-	-
↑ Potassium	2.3	1.2	1.2	-
↓ Potassium	-	1.2	-	-
↑ Sodium	-	-	-	-
↓ Sodium	14.6	-	-	-
↑ Triglycerides	N/D	11.5	-	-
Cholesterol*	21.1	4.4	-	-
↓ Hemoglobin	-	-	-	1.2
↓ Neutrophil count	8.1	2.7	-	-
↓ Platelet count	-	-	-	-

* American Heart Association grading
NP: not performed by sponsor
(Source: FDA Analysis of NV15355)

Reviewer's Comments

1. An exploratory analysis was performed using a z-test to detect differences in treatment arms with regard to proportions of patients with abnormal laboratory shifts from grade 0 to grade 1 and 2. The results showed significant differences ($p<0.01$) in the proportion of patients with low-grade elevation of GGT (15.7% in SQV-SGC vs. 1.7% in SQV-HGC), and low-grade decrease of blood glucose (16.7% in SQV-SGC vs. 8.4% in SQV-HGC). For further comments on these abnormal laboratory results, please refer to sections 8.2.10.4.4.1 and 8.2.10.4.4.5.

2. One patient on the SQV-HGC treatment arm had triglyceride shift from a grade 0 to grade 2, and one from grade 2 to grade 4. In the SQV-SGC arm, 9 patients had triglyceride shift from grade 0 to grade 2. The exploratory z-test for this

laboratory parameter was also significant ($p<0.01$).

8.3.10.4.4.2. Marked Laboratory Abnormalities

Data on marked laboratory abnormalities are summarized in Table 8.3.10.4.4.2. Relatively few patients on the SQV-HGC arm had marked laboratory abnormalities with the exception of decreased glucose (2%) and neutropenia (2%). Higher incidences involving more laboratory parameters were seen in the SQV-SGC group.

Table 8.3.10.4.4.2. Summary of Marked Laboratory Abnormalities

Analyte	Number of Patients with Marked Laboratory Abnormalities			
	SQV-HGC Treatment Arm (N = 81)		SQV-SGC Treatment Arm (N = 90)	
	n	(%)	n	(%)
↓ Glucose	2	(2.5)	3	(3.3)
↑ CK	-	-	3	(3.3)
↑ GGT	-	-	2	(2.2)
↑ ALT (SGPT)	-	-	1	(1.1)
↑ Potassium	-	-	1	(1.1)
↓ Hemoglobin	2	(2.5)	-	-
↓ Neutropenia	-	-	1	(1.1)

(Source: NV15355)

Reviewer's Comment

Although the incidence of elevated CK was higher in the SQV-HGC group, more patients experienced markedly increased CK levels in the SQV-SGC group. As previously noted (see section 8.2.10.4.4.1), CK elevation could result from a number of causes ranging from HIV-associated or drug-induced myopathy to trauma.

8.3.10.4.4.3. Laboratory Abnormalities Associated with Premature Discontinuation of Treatment

According to the sponsor, there were no cases of premature withdrawal from the study due to laboratory abnormalities during the study period.

8.3.10.4.5. Overdosage Exposure

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

8.3.10.5. Efficacy Outcomes

The efficacy results as presented by the sponsor are summarized in the following section. For a comprehensive review, please refer to FDA statistical review by Dr. Greg Soon.

8.3.10.5.1. HIV RNA Level

Table 8.3.10.5.1.A summarizes the change from baseline of log_{10} HIV RNA in both treatment arms. The maximum mean suppression of log_{10} HIV RNA for the SQV-HGC arm occurred at week 8 (-1.83). At week 16 the mean suppression in this arm was -1.56. The SQV-SGC arm achieved a maximum mean suppression of -1.96 at week 12 and the level remained unchanged at week 16.

The primary efficacy analysis was to detect treatment differences by comparing the AUCMB of log_{10} HIV RNA from both treatment arms at week 16. The AUCMB of SQV-HGC group was -1.5 and that of SQV-SGC was -1.6 (see Table 8.3.10.5.1.B). For this parameter, there was no statistically significant difference between the two treatment arms ($p = 0.19$).

Table 8.3.10.5.1.C summarizes the secondary efficacy analysis of the proportion of patients with HIV RNA below the limit of quantification; i.e. less than 400 copies/mL. According to the sponsor, 80% of patients in the SQV-SGC group had viral levels below 400 copies/mL compared to 43% in the SQV-HGC group at week 16 based on the intent-to-treat population. The difference was statistically significant ($p = 0.001$). In the "worse-case" analysis; i.e., when missing HIV RNA results were assumed to represent viral load above the level of detection, the proportions of patients with HIV RNA below 400 copies/mL were 67% for the SQV-SGC arm and 37% for the SQV-HGC arm. The difference, in this analysis, was also statistically significant ($p = 0.001$).

Table 8.3.10.5.1.A. Summary of Log_{10} HIV RNA (copies/mL) Change from Baseline

Log_{10} HIV RNA	Week 4	Week 8	Week 12	Week 16
SQV-HGC				
N	74	71	75	69
Mean	-1.80	-1.83	-1.72	-1.56
Standard deviation	0.49	0.57	0.63	0.63
Minimum	-2.91	-3.27	-3.27	-2.83
Maximum	-0.13	-0.32	0.39	0.30
Median	-1.83	-1.87	-1.77	-1.58
Interquartile range				
SQV-SGC				
N	83	79	78	75
Mean	-1.74	-1.92	-1.96	-1.96
Standard deviation	0.54	0.60	0.67	0.66
Minimum	-3.03	-3.27	-3.27	-3.27
Maximum	0.44	0.44	0.26	0.17
Median	-1.84	-2.02	-1.99	-1.99
Interquartile range				

(Source: NV15355)

Table 8.3.10.5.1.B. Summary of AUCMB of Log10 HIV RNA (copies/mL) to Week 16

AUCMB16 (Log_{10} HIV RNA)	SQV-HGC	SQV-SGC
N	78	86
Mean	-1.5	-1.6
Standard deviation	0.4	0.5
Minimum	-2.3	-2.8
Maximum	-0.1	0.2
Median	-1.5	-1.7
Interquartile range		
Difference probability p-value = 0.1929		

(Source: NV15355)

Table 8.3.10.5.1.C. Summary of Proportion of Patients with HIV RNA below the limit of Quantification

Treatment	Number of Patients with HIV RNA <400 copies/mL									
	Week 0		Week 4		Week 8		Week 12		Week 16	
	n	%	n	%	n	%	n	%	n	%
SQV-HGC	0/81	0	25/74	34	41/71	58	33/75	44	30/69	43
SQV-SGC	0/90	0	29/83	35	57/79	65	60/78	77	60/75	80
									(p = 0.001)	

(Source: NV15355)

Reviewer's Comments

1. The sponsor failed to show a statistically significant difference in the AUCMB16 of log_{10} HIV RNA between the two treatment arms. Nevertheless, at week 16, the proportion of patients with viral load below the level of detection (<400 copies/mL) in the SQV-SGC arm was significantly higher than that in the SQV-HGC arm. The discrepancy was most likely due the fact that (1) both treatment regimens were equally effective in reducing the viral load in naive patients during the initial few weeks of treatment, and (2) the analyses were performed after a relatively short treatment period. The results show that the proportion of patients with HIV RNA below quantification limit is a sensitive parameter for assessing drug activity, particularly when potent therapeutic regimens are used.

2. The sponsor's intent-to-treat population did not include patients with missing baseline HIV RNA values and/or HIV RNA values during treatment period. Therefore, patients who discontinued treatment due to adverse events were also excluded from the analysis for viral suppression. In FDA analysis, the intent-to-treat population included all randomized patients who had received at least one dose of study drugs; i.e., n = 90 for the SQV-SGC arm, and 81 for the SQV-HGC arm. Based on this analysis, the percentages of patients with HIV RNA <400 copies/mL for the SQV-SGC arm and the SQV-HGC arm at week 16 were 66.7% and 37.0%, respectively. See statistical review by Dr. Greg Soon for more details.

8.3.10.5.1.2. CD4 Cell Count

The changes of CD4 cell count from the baseline are summarized in Table 8.3.10.5.2.A. At week 16, the mean increase of CD4 cell count was 114.7

cells/mm^3 in the SQV-HGC treatment arm and 96.5 cells/mm^3 in the SQV-SGC arm. The difference in CD4 cell counts between the two treatment arms was not statistically significant.

The AUCMB16 of the SQV-HGC was 63.6 cells/mm^3 and that of SQV-SGC was 43.9 cells/mm^3. The data on AUCMB of CD4 cell count from both treatment arms are summarized in Table 8.3.10.5.2.B.

Table 8.3.10.5.2.A. Summary of CD4 Cell Count (cells/mm^3) Change from Baseline

CD4 Cell Count	Week 4	Week 8	Week 12	Week 16
SQV-HGC				
N	76	71	74	70
Mean	63.1	75.2	66.9	114.7
Standard deviation	130.0	118.3	114.3	122.1
Minimum	-341.0	-151.0	-386.0	-335.0
Maximum	378.0	610.0	328.0	376.0
Median	69.5	60.0	74.0	103.3
Interquartile range				
SQV-SGC				
N	80	77	78	73
Mean	34.6	51.4	64.5	96.5
Standard deviation	138.9	155.0	145.3	151.9
Minimum	-585.5	-585.5	-632.5	-226.0
Maximum	370.5	424.0	449.0	673.0
Median	36.5	79.5	63.0	85.0
Interquartile range				

(Source: NV15355)

Table 8.3.10.5.2.B. Summary of AUCMB of CD4 Cell Count to Week 16 (ITT Population)

AUCMB16 (CD4 cell Count)	SQV-HGC	SQV-SGC
N	78	85
Mean	63.6	43.9
Standard deviation	84.5	101.9
Minimum	-200.4	-2.8
Maximum	255.5	476.4
Median	72.7	278.7
Interquartile range		

(Source: NV15355)

8.3.11. Conclusions

This open-label trial was conducted primarily to compare the efficacy of SQV-SGC to SQV-HGC in combination with two other antiretroviral drugs for a relatively short duration (16 weeks). While there was no statistically significant difference between treatment arms in terms of HIV RNA $AUCMB_{16}$, patients in the SQV-SGC group had numerically greater degree of viral suppression than those in the SQV-HGC group. The proportion of patients with HIV RNA levels below 400 copies/mL was significantly larger in the SQV-SGC group. Both treatment arms demonstrated sustained increases in the CD4 cell count.

There were no unexpected treatment-emergent adverse events reported in either treatment group. The safety profile was similar to that seen in study NV15182. The frequency of adverse events was higher in the SQV-SGC group, with nausea, diarrhea, flatulence, dyspepsia, abdominal discomfort and headache being the most common. A disproportionally higher proportion of patients (10%) in the SQV-SGC treatment arm withdrew prematurely from the study primarily due to gastrointestinal adverse events compared to that in the SQV-HGC arm (1.2%). Low-grade elevations of transaminases, amylase, creatine kinase and mild hyponatremia were also evident in the study population. The SQV-SGC treatment group had a higher frequency of grade 0 to 2 shifts of triglycerides than that of the SQV-HGC group (11.5% versus 1.4%, respectively).

8.4. Protocol NV14256

Protocol NV14256 was a clinical endpoint study conducted with the SQV-HGC formulation. The results of this study were previously submitted under NDA 20-628. In accordance to prior agreement with the FDA, the sponsor submitted this study to support full approval for this current NDA 20-828. Reference is made to NDA 20-628 for full review of this study.

8.5. Protocol EV14757

Protocol EV14757 was an open-label study with high-dose SQV-HGC regimens. The results of this study were previously submitted under NDA 20-628. Reference is made to NDA 20-628 for full review of this study.

9. SUMMARY OF SAFETY AND EFFICACY

9.1. Safety

9.1.1. Adverse Events

The sponsor submitted the results from three clinical studies (NV15107, NV15182 and NV15355) involving 609 HIV-infected patients exposed to SQV-SGC to demonstrate its safety profile when used as monotherapy or in combination with other nucleoside antiretroviral drugs. The 24-week and 48-week safety data from study NV15182 comprised most of the safety data.

The vast majority of patients experienced treatment-emergent clinical adverse events. According to the sponsor, 91.2% and 94.1% of 442 patients in the safety study 15182 had one or more adverse events after 24 and 48 weeks of treatment, respectively. A total of 85% of 88 patients in study NV15107 reported at least one adverse event during the 48-week study period. In the first 16-week comparative phase of study NV15355, 88% of patients on SQV-SGC treatment arm experienced one or more adverse event compared to 85% on the SQV-HGC arm. The majority of these adverse events appeared to be of mild to moderate intensity. The most frequently reported adverse events, excluding those regarded by the investigators as "unrelated to treatment," were primarily gastrointestinal disturbances; i.e., diarrhea, nausea, dyspepsia, flatulence, and vomiting. In addition, abdominal pain, abdominal discomfort, headache and fatigue were common adverse events affecting the body as a whole. Depression, insomnia, anxiety, taste alteration and skin rashes were among the less frequently reported complaints. The 48-week report of study NV15182 showed the following

proportions of patients with treatment-emergent adverse events: diarrhea, 38.2%; nausea, 24.4%; dyspepsia, 20.0%; abdominal discomfort, 17.2%; headache, 12.2%; fatigue, 12.2% and flatulence, 11.8%. It should be noted that the concomitant use of other nucleoside antiretroviral drugs was permitted in these trials. Most of these drugs have also been associated with adverse effects similar to those listed above.

A total of 8.6% of patients prematurely withdrew from study NV15182 by 48 weeks of treatment due to adverse events. Most of these patients experienced moderate to severe symptoms frequently from multiple concurrent adverse events. The adverse events of at least moderate intensity occurring in 2% or more of patients in all three studies are summarized in Table 9.1.1. In the comparative study NV15355, the frequency of adverse events were higher in the SQV-SGC treatment arm for all adverse event categories when compared to that of the SQV-HGC arm.

In summary, treatment-emergent adverse events occur in higher number of patients on SQV-SGC combination therapy than that observed for SQV-HGC. However, they are well tolerated by the majority of patients. No deaths attributable to SQV-SGC treatment or overdosage exposures have been reported to date.

9.1.2. Laboratory Abnormalities

A significant proportion of patients in all three studies (NV15107, NV15182, NV15355) had low-grade elevations of ALT and AST. The percentages of patients on SQV-SGC combination regimens with abnormal transaminases ranged from approximately 8% after 16 weeks of treatment to 23% at week 48. The GGT and bilirubin elevations appeared to mirror the ALT and AST levels. Low-grade elevation of alkaline phosphatase was also seen in a small number of patients and could indicate mild hepatobiliary toxicity. Other low-grade laboratory abnormalities including elevated creatine kinase, elevated amylase, decreased glucose, hyponatremia and neutropenia also occurred with relatively high frequency (approximately 10% to 29%). According to the sponsor, most of these abnormalities were isolated events of no clinical consequences.

A smaller number of patients (less than 7%) experienced high-grade shifts of these laboratory parameters (Table 9.1.2). Nevertheless, the differences in the proportions of patients with marked laboratory abnormalities between week 24 and 48 were negligible. Only 4 patients (<1%) from study NV15182 withdrew from the study as a result of abnormal laboratory tests after 48 weeks, and none from NV15355 by week 16.

A substantial proportion of patients (25% in NV15182 and 42% in NV15107) had non-fasting triglycerides of 400 mg/dL (ACTG grade 2) or above. Although the baseline values in these cases were unknown, the prevalence and severity of hypertriglyceridemia may not be due to dietary influence as suggested by the sponsor. In study NV15355, approximately 11% of patients on SQV-SGC treatment arm had elevated triglycerides from the baseline compared to 1% the SQV-HGC arm after 16 weeks.

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Table 9.1.1. Percentage of Patients with Treatment-Emergent[1] Adverse Events of At Least Moderate Intensity Reported in ≥2% of Patients

Adverse Events	NV15107[2] PI naive patients				NV15182[3] PI-naive patients (75%)	NV15355[4] Treatment-naive patients[5]	
	600 mg TID SQV-HGC + 2 RTIs (n = 11)	400 mg TID SQV-SGC + 2 RTIs (n = 12)	800 mg TID SQV-SGC + 2 RTIs (n = 33)	1200 mg TID SQV-SGC + 2 RTIs (n = 32)	1200 mg TID SQV-SGC + 2 RTIs (n = 442)	600 mg TID SQV-HGC + 2 RTIs (n = 81)	1200 mg TID SQV-SGC + 2 RTIs (n = 90)
Body as a whole							
Fatigue	-	-	15.2	-	6.8	6.2	6.7
Headache	-	-	18.2	9.4	7.9	4.9	8.9
Abd. discomfort	-	-	18.2*	15.6*	8.8	4.9	13.3
Abd. pain	-	-	-	-	4.3	1.2	7.8
Fever	-	-	-	9.4	-	-	-
Gastrointestinal							
Diarrhea	27.3	-	24.4	28.1	20.8	12.3	15.6
Nausea	-	33.3	18.2	12.5	10.4	13.6	17.8
Dyspepsia	-	-	15.2	12.5	8.8	2.5	10.0
Flatulence	-	-	-	-	5.9	7.4	12.2
Vomiting	-	-	-	-	3.4	1.2	4.4
Constipation	-	-	-	-	-	-	3.3
Psychiatric							
Depression	-	-	-	-	2.9	-	-
Insomnia	-	-	-	-	2.5	1.2	5.6
Anxiety	-	-	-	-	-	2.5	2.2
Libido disorder	-	-	-	-	-	-	2.2
Musculoskeletal							
Pain	-	-	-	-	-	3.7	3.3
Arthralgia	-	-	12.1	-	-	-	-
Myalgia	-	-	9.1	-	-	-	-
Nervous							
Taste alteration	-	-	-	-	-	1.2	4.4
Dermatological							
Rash	-	-	12.1	15.6	2.0	4.9	-
Others							
Verruca	-	-	-	-	-	-	2.2

[1] Includes adverse events at least possibly related to study drug or of unknown relationship (except for NV15107 where all causalities are included).
[2] Data from 8-week analysis.
[3] Data from 48-week analysis.
[4] Data from 16-week analysis.
[5] Protease-inhibitor naive and ≤4 weeks of treatment with any nucleoside antiretroviral drug.
* Includes "abdominal discomfort" and "abdominal pain."

Table 9.1.2. Percentage of Patients with marked laboratory abnormalities[1] in ≥2% of Patients

Analyte	NV15182[3] PI-naive patients (75%)	NV15355[4] Treatment-naive patients[5]	
	1200 mg TID SQV-SGC + 2 RTIs (n = 442)	600 mg TID SQV-HGC + 2 RTIs (n = 81)	1200 mg TID SQV-SGC + 2 RTIs (n = 90)
↑ ALT (SGPT)	2.9	-	1.1
↑ AST (SGOT)	2.0	-	-
↑ GGT	N/A	-	2.2
↑ Creatine kinase	2.9	-	-
↑ Amylase	0.2	N/P	N/P
↑ Total bilirubin	1.1	-	-
↑ Glucose	0.7	-	-
↓ Glucose	5.4	2.5	3.3
↑ Potassium	1.6	-	1.1
↑ Sodium	0.2	-	-
↓ Hemoglobin	-	-	-
↓ Neutrophils	0.5	2.5	1.1
↓ Platelets	0.2	-	-

[1] Defined as a shift from grade 0 at baseline to at least grade 3, or from grade 1 to grade 4.
[2] Data from 8-week analysis.
[3] Data from 24-week analysis.
[4] Data from 16-week analysis.
[5] Protease-inhibitor naive and ≤4 weeks of treatment with any nucleoside antiretroviral drug.
N/P: not performed

9.2. Efficacy

SQV-SGC treatment is associated with improvement of CD4 cell counts and suppression of HIV RNA replication in a majority of patients. The virologic and immunologic responses are greater than those seen with the SQV-HGC formulation. The 48-week analysis of study NV15182 showed approximately 14% of patients on SQV-SGC prematurely withdrew from the study as a result of "insufficient therapeutic response." Using standardized evaluation criteria, study NV15355 reported no premature discontinuations due to lack of virologic therapeutic response by week 16 for both SQV-SGC and SQV-HGC arms.

9.2.1. CD4 Cell Count

The sponsor demonstrated that treatment regimens with SQV-SGC improved patients' CD4 cell counts. In study NV15182, the mean baseline CD4 cell count was 221 cells/mL. After 24 weeks of treatment, approximately 84% of patients had improvement of CD4 cell counts with a mean increase of 80 cells/mL.

The CD4 increase was subsequently confirmed by study NV15355. In this study, the mean baseline CD4 cell counts were 408 cells/mL and 447 cells/mL for the SQV-HGC and SQV-SGC treatment arms, respectively. At week 16, both treatment arms showed comparable CD4 cell count improvement. The SQV-HGC arm had a mean CD4 cell count increase of 115 cells/mL, while the mean increase in the SQV-SGC arm was 96 cells/mL.

9.2.2. HIV RNA level

The majority of patients in study NV15182 were antiretrovirally experienced (96%), although 82% of them were naive to protease-inhibitors. At week 24 of this study, the mean change from baseline of HIV RNA level was -0.86 $\log_{10}$ copies/mL. However, in the subgroup of protease-inhibitor experienced patients, the mean change from baseline of HIV RNA was only -0.46 $\log_{10}$ copies/mL. While approximately 43% of all patients had HIV RNA levels below limit of quantification after 24 weeks of therapy, the percentages in the above subgroup was significantly lower (28%). Patients who added new reverse transcriptase inhibitor(s) appeared to have numerically larger proportion of patients with HIV RNA below quantifiable limit.

Study NV15355 enrolled treatment naive patients or those who had minimal exposure to reverse transcriptase inhibitors (≤ 4 weeks). Patients on both treatment arms had greater reduction of HIV RNA compared to that reported for treatment-experienced patients in NV15182. The mean change from baseline at week 16 was -2.0 $\log_{10}$ copies/mL and -1.6 $\log_{10}$ copies/mL for the SQV-SGC and the SQV-HGC, respectively. The AUCMB analysis of $\log_{10}$ HIV RNA values failed to show statistically significant difference between the two treatment arms. However, the percentages of patients with HIV RNA below detection limit showed a statistically significant difference between the two arms which favored the SQV-SGC treatment; i.e., 67% in the SQV-SGC arm and 37% in the SQV-HGC arm.

Reviewer's Comment

The sponsor recently submitted unexpected pharmacokinetic findings on SQV plasma concentrations in some patients from study NV15182 who had been on long-term SQV-SGC therapy (>36 weeks). Analyses of the mean SQV AUC in these patients showed significant reduction (51% to 76%) compared to the previously known mean steady-state SQV AUC in two separate cohorts of patients (n =21 and n = 11). While the sponsor stated that the lower SQV exposure showed no effect on viral suppression, the available data presented by the sponsor neither supported nor confirmed this conclusion. In-depth pharmacokinetic and clinical studies to further delineate this aberrant phenomenon are obviously needed. The sponsor has agreed to conduct further studies to elucidate this issue as phase 4 commitments. Please also see Reviewer's Comment in section 6.3.1. for further details.

10. CONCLUSIONS

SQV-SGC (Fortovase™) is an improved formulation of saquinavir with approximately 3-fold increase in bioavailability over the currently marketed SQV-HGC formulation. Data from three studies conducted with SQV-SGC (NV15107, 15182 and 15355) appear to support a conclusion that SQV-SGC is safe, well tolerated, and effective in suppressing HIV RNA replication and improving the CD4 cell count in a majority of patients.

The principal treatment-emergent adverse events associated with SQV-SGC therapy in combination with other antiretroviral agents are primarily gastrointestinal disorders; i.e., diarrhea, nausea, vomiting, dyspepsia, and flatulence. Additional clinically significant adverse events are abdominal discomfort, headache and fatigue. The evidence to date shows only approximately 9% of patients who prematurely discontinued treatment due to adverse events.

SQV-SGC therapy is associated with abnormal liver function tests, elevated creatine kinase, hyperamylasemia, hyponatremia, hypoglycemia, hyperglycemia, and neutropenia in a relatively high number of patients. These abnormal laboratory parameters, however, are mostly mild to moderate in severity, and are similar in profile to those seen in previous SQV-HGC studies. Less than 1% of patients has been taken off study treatment due to significant laboratory abnormalities (persistently elevated liver function tests, elevated creatine kinase, and thrombocytopenia). The emergence of hypertriglyceridemia in a significant number of study patients appears clinically significant and should require periodic monitoring to avoid the risks of pancreatitis and cardiovascular disease.

Hypertriglyceridemia has also been observed with ritonavir therapy. It is of interest to determine whether there is a definitively link between the use of protease inhibitors and triglyceride elevation.

In combination therapy with other antiretroviral agents, SQV-SGC has been shown to be superior to SQV-HGC in study NV15355 with respect to the percentage of patients having viral suppression below the level of quantification (HIV RNA<400 copies/mL). Sixty-seven percent of patients on SQV-SGC treatment compared to 37% on SQV-HGC treatment had HIV RNA level below detection limit. Both treatment arms showed comparable sustained improvements in CD4 cell counts. Data on clinical benefits from previous studies with SQV-HGC formulation also demonstrate the long-term clinical benefits; i.e., reduction of mortality and AIDS-defining clinical events, provided by saquinavir therapy.

The pharmacokinetic issues regarding the lower-than-expected plasma AUC of SQV in long-term therapy are still unresolved at this time. The effects of this lower SQV plasma concentration on virological and immunological responses are currently under review.

In conclusion, the clinical and laboratory risks associated with SQV-SGC treatment, while not insignificant and inconsequential, appear to be reasonably acceptable. There is preponderant evidence that SQV-SGC can suppress HIV RNA replication and improve CD4 cell count to greater degrees than those achieved by the SQV-HGC formulation. With the demonstrated clinical benefits from previous studies of SQV-HGC, together, the risk-benefit comparison favors the approval of SQV-SGC for marketing.

11. LABELING

A final labeling draft was submitted to the FDA on 5 November 1997. The draft was approved with minor modifications.

12. PHASE 4 COMMITMENTS

The sponsor recently submitted phase 4 commitment plan as outlined below:

13. REGULATORY RECOMMENDATION

The undersigned reviewers recommend this application, NDA 20-828, for approval under CFR 314.510.

Kimberly Struble, RPh
RRO/DAVDP/HFD-530/FDA

Tan T. Nguyen
MO/DAVDP/HFD-530/FDA

Concurrences:

HFD-530/ActDivDir/Birnkrant
HFD-530/SMO/Murray

cc:

NDA 20-828
HFD-530/ActDivDir/Birnkrant
HFD-530/SMO/Murray
HFD-530/SMO/Gitterman
HFD-530/MO/Nguyen
HFD-530/CR/Struble
HFD-530/Chem/Liu
HFD-530/PharmTox/Wu
HFD-530/Biopharm/Rajagopalan
HFD-530/Microbiol/Battula
HFD-530/Stat/Soon
HFD-530/CSO/Kelly

ADDENDUM TO SECTION 9.2.9.4.2
NDA 20-828

DRAFT

48-Week Safety Update of NV15182

The sponsor submitted the 48-week safety update for NV15182 on 6/18/97. A review of the sponsor's data is presented in this addendum.

1. Patient Disposition

The sponsor reported that 307 patients (69.5%) completed at least 48 weeks of treatment, and the number of study discontinuations has risen to 139 patients. While the most common reason for early withdrawals in the 24-week analysis was treatment intolerance, the most common reason in the 48-week analysis was insufficient therapeutic response. Table 1 shows the disposition of dropouts.

Table 1. Summary of Premature Discontinuations of Treatment (N=442)

Reason	Sponsor's Analysis		FDA Analysis	
	n	%	n	%
Insufficient therapeutic response	61	(13.8)	64	(14.5)
Adverse event/intercurrent illness	36	(8.1)	38	(8.6)
Refused treatment/non-cooperation/withdrew consent	26	(5.9)	22	(5.0)
Lost to follow-up	7	(1.6)	8	(1.8)
Laboratory toxicity	4	(0.9)	4	(0.9)
Miscellaneous	3	(0.7)	-	-
Protocol violation	-	-	1	(0.2)
Death on therapy	2	(0.5)	1	(0.5)
Death off therapy	-	-	6	(0.5)

(Source: NV15182, 48-Week Safety Update)

Reviewer's Comment

1. The investigators' criteria for discontinuing patients based on "insufficient therapeutic response" varied greatly. For example, patient 17167/2094 had progressive reduction of HIV RNA from 48,280 copies/mL at baseline to 920 on day 253. The CD4 cell counts improved from 410 cells/mm^3 to 730 during the same time. This patient was considered to have "insufficient therapeutic response" and was discontinued from the study on day 253. On the other hand, patient 17055/2842 had HIV RNA levels ranging from copies/mL

and progressively decreased CD4 cell counts during the study. This patient was not considered to have treatment failure by a different investigator until day 183.

2. Patient 16993/2272 was counted by the sponsor as "refused treatment/non-compliance/withdrew consent." Record review showed that the patient's treatment was discontinued on day 71 after an episode of acute viral hepatitis. The investigator attributed his discontinuation as due to adverse event/intercurrent illness. This reviewer agreed with the investigator's assessment and reclassified this case as "adverse event."

3. Patient 16979/2683 withdrew from the study on day 239 due to concern about insufficient virological response and not due to "refused treatment/non-cooperation/withdrew consent" as indicated by the investigator. The case was reclassified by this reviewer as "insufficient therapeutic response."

4. Patient 17046/2115 dropped out of the study due to intestinal MAI thought to cause decreased absorption of SQV-SGC; hence, poor virologic response. The patient was placed on indivavir. There was no indication that the patient was not be able to tolerate the study medication. This case was reclassified by this reviewer as "insufficient therapeutic response," and not as "adverse event."

5. Patient 17194/2625 withdrew from the study due to "severe depression" (with suicide ideation) concerning his increasing viral load. The viral load progressively increased from 7280 copies/mL at base line to 67,340 copies/mL on day 120, while no improvement on CD4 cell counts was demonstrated. The reason for withdrawal was reclassified as "insufficient therapeutic response" by this reviewer in the absence of other significant adverse events.

6. The reason for premature withdrawal of patient 16989/2381 was listed as "refused treatment/non-cooperation/withdrew consent." At the time of withdrawal, patient had acute pancreatitis and "serious" diabetes mellitus. The baseline glucose was normal and subsequently became elevated during the study. This reviewer believes that the reason for withdrawal was "adverse event/intercurrent illness."

7. Patient 16993/2272 was classified by the sponsor as "refused treatment/non-cooperation/withdrew consent." The investigator gave the reason for withdrawal in the CRF as "loss to follow-up" and "adverse events." At the time, patient had acute hepatitis B with grade 4 elevation of liver function enzymes. This case was reclassified by this reviewer as "adverse event/intercurrent illness."

8. Of the three patients listed in the "miscellaneous" category, the following reasons were given: one patient could not return for follow-up due to an extended trip outside or the country; one was considered "noncompliance" by the

investigator; and the third took forbidden medication. These cases were reclassified as "lost to follow-up," "noncompliance" and "protocol violation" by this reviewer.

2. Drug Exposure

The number of patients remaining on treatment at each time point is shown in Table 2.A. The extent of drug exposure is summarized in Table 2.B.

Table 2.A. Number of Patients Remaining on Treatment (N=442)

Treatment Duration	Number of Remaining Patients	
	n	%
4 weeks	424	(95.9)
8 weeks	409	(92.5)
16 weeks	396	(89.6)
24 weeks	373	(84.4)
28 weeks	358	(81.0)
32 weeks	350	(79.2)
36 weeks	342	(77.4)
40 weeks	330	(74.7)
44 weeks	315	(71.3)
48 weeks	307	(69.5)

(Source: NV15182, 48-Week Safety Update)

Table 2.B. Summary of Treatment Duration (N=442)

	Treatment Duration (week)
Mean	43.1
Standard deviation	15.8
Median	52.1
Range	

(Source: NV15182, 48-Week Safety Update)

3. Adverse Events

3.1. Overviews of Adverse Events

The 48-week adverse event profile was similar to that reported in the 24-week analysis. The incidences of adverse events, however, increased slightly in all categories. No new adverse events were apparent after 48 weeks of treatment.

The most common adverse events overall were diarrhea (46.2%), nausea (29.6%), and dyspepsia (21.5%). A significant number of patients also experienced abdominal symptoms ranging from "discomfort" (19%) to "pain" (9.5%). The frequencies of headache, fatigue and skin rash were 17.6%, 17.4%, and 13.1%, respectively. Insomnia was reported in 5.7% of patients, depression in 7.7%, and anxiety in 5.0%. The frequencies of adverse events thought to be related to treatment were slightly less than the above figures (see Table 3.1.A). The majority of treatment-related adverse events were of mild to moderate intensity. Based on the reported data, diarrhea was the only drug-related adverse effect with severe intensity occurring in 2% or more of patients after 48 weeks.

Table 3.1.B shows the treatment-emergent adverse events, classified by intensity, in 2% or more of patients. Table 3.1.C summarizes the treatment-emergent adverse events of at least moderate intensity observed in 2% or more of patients.

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Table 3.1.A. Summary of Treatment-Emergent Adverse Events Reported in ≥2% of Patients

Body System/Disorder	Number of Patients with Adverse Events			
	Total (N=442)		Excluding those unrelated to drug[1]	
	n	%	n	%
Body as a whole				
Abdominal discomfort	84	(19.0)	76	(17.2)
Headache	78	(17.6)	54	(12.2)
Fatigue	77	(17.4)	54	(12.2)
Abdominal pain[2]	42	(9.5)	35	(7.9)
Fever	42	(9.5)	9	(2.0)
Night sweats	26	(5.9)	12	(2.7)
Trauma	24	(5.4)	1	(0.2)
Decreased appetite	21	(4.8)	13	(2.9)
Weight loss	20	(4.5)	7	(1.6)
Chest pain	12	(2.7)	3	(0.7)
Dyspnea	11	(2.5)	4	(0.9)
Allergic reaction	11	(2.5)	4	(0.9)
Asthenia	11	(2.5)	10	(2.3)
Edema	10	(2.3)	2	(0.5)
Shivering	10	(2.3)	5	(1.1)
Gastrointestinal				
Diarrhea	204	(46.2)	169	(38.2)
Nausea	131	(29.6)	108	(24.4)
Dyspepsia	95	(21.5)	88	(20.0)
Flatulence	53	(12.0)	52	(11.8)
Vomiting	43	(9.7)	29	(6.6)
Constipation	19	(4.3)	13	(2.9)
Tooth disorder	13	(2.9)	2	(0.5)
Buccal mucosa ulceration	12	(2.7)	4	(0.9)
Central/peripheral nervous				
Dizziness	18	(4.1)	9	(2.0)
Extremity numbness	18	(4.1)	10	(2.3)
Paresthesia	17	(3.8)	8	(1.8)
Peripheral neuropathy	16	(3.6)	11	(2.5)
Neuropathy NOS	10	(2.3)	8	(1.8)
Dermatological				
Rash	58	(13.1)	22	(5.0)
Pruritus	23	(5.2)	12	(2.7)
Skin disorder NOS	16	(3.6)	3	(0.7)
Folliculitis	13	(2.9)	3	(0.7)
Xeroderma	10	(2.3)	4	(0.9)
Musculoskeletal				
Musculoskeletal pain	26	(5.9)	6	(1.4)
Back pain	25	(5.7)	5	(1.1)
Arthralgia	18	(4.1)	7	(1.6)
Myalgia	15	(3.4)	6	(1.4)
Pain NOS	10	(2.3)	3	(0.7)

(Continuing...)

Table 3.1.A. (Cont.) Summary of Treatment-Emergent Adverse Events Reported in ≥2% of Patients

Body System/Disorder	Number of Patients with Adverse Events			
	Total (N=442)		Excluding those unrelated to drug[1]	
	n	%	n	%
Respiratory				
Sinusitis	44	(10.0)	5	(1.1)
Rhinitis	43	(9.7)	2	(0.5)
Cough	32	(7.2)	7	(1.6)
Pharyngitis	14	(3.2)	1	(0.2)
Allergic rhinitis	10	(2.3)	0	-
Psychiatric				
Depression	34	(7.7)	15	(3.4)
Insomnia	25	(5.7)	17	(3.8)
Anxiety	22	(5.0)	8	(1.8)
Resistance mechanism				
Upper resp. tract infection	53	(12.0)	4	(0.9)
Influenza	49	(11.1)	6	(1.4)
Candidiasis	22	(5.0)	0	-
Herpes simplex	22	(5.0)	2	(0.5)
Herpes zoster	17	(3.8)	2	(0.5)
Miscellaneous				
Taste alteration[3]	13	(2.9)	12	(2.7)
Visual disturbance	12	(2.7)	2	(0.5)
Conjunctivitis	11	(2.5)	3	(0.7)
Otitis	12	(2.7)	1	(0.2)
Micturition	9	(2.0)	3	(0.7)

[1] Includes those adverse events of unknown relationship to treatment.
[2] Includes "abdominal pain" and "colic abdomen" as coded by sponsor.
[3] Includes "taste alteration" and "taste unpleasant" as coded by sponsor.
NOS: Not otherwise specified by sponsor.
(Source: FDA Reviewer's analysis of NV15182, 48-week Safety Update)

Table 3.1.B. Summary of Treatment-Emergent Adverse Events[1] Classified by intensity Reported in ≥2% of Patients

Body System/Disorder	Total (N=442)		Mild		Moderate		Severe		Life-threatening		Unknown Intensity[1]	
	n	%	n	%	n	%	n	%	n	%	n	%
Body as a whole												
Abdominal discomfort	76	(17.2)	37	(8.4)	14	(3.1)	7	(1.6)	-		18	(4.1)
Headache	54	(12.2)	19	(4.3)	24	(5.4)	3	(0.7)	-		8	(2.0)
Fatigue	54	(12.2)	24	(5.4)	16	(3.6)	2	(0.5)	-		12	(2.7)
Abdominal pain[2]	35	(7.9)	16	(3.6)	7	(1.6)	6	(1.4)	-		6	(1.4)
Decreased appetite	13	(2.9)	6	(1.4)	3	(0.7)	-		-		4	(0.9)
Night sweats	12	(2.7)	8	(1.8)	2	(0.5)	-		-		2	(0.5)
Asthenia	10	(2.3)	6	(1.4)	1	(0.2)	-		-		3	(0.7)
Gastrointestinal												
Diarrhea	169	(38.2)	77	(17.4)	55	(12.4)	9	(2.0)	-		28	(6.3)
Nausea	108	(24.4)	62	(14.0)	28	(6.3)	7	(1.6)	-		11	(2.5)
Dyspepsia	88	(20.0)	49	(11.1)	21	(4.8)	2	(0.5)	-		16	(3.6)
Flatulence	52	(11.8)	26	(5.9)	9	(2.0)	4	(0.9)	-		13	(2.9)
Vomiting	29	(6.6)	14	(3.2)	11	(2.5)	3	(0.7)	-		1	(0.2)
Constipation	13	(2.9)	7	(1.6)	5	(1.1)	-		-		1	(0.2)
Dermatological												
Rash	22	(5.0)	13	(2.9)	6	(1.4)	-		-		3	(0.7)
Pruritus	12	(2.7)	5	(1.1)	4	(0.9)	-		-		3	(0.7)
Psychiatric												
Insomnia	17	(3.8)	6	(1.4)	5	(1.1)	-		-		6	(1.4)
Depression	15	(3.4)	2	(0.5)	4	(0.9)	-		-		9	(2.0)
Peripheral nervous												
Peripheral neuropathy	11	(2.5)	4	(0.9)	1	(0.2)	-		-		6	(1.4)
Extremity numbness	10	(2.3)	6	(1.4)	1	(0.2)	-		-		3	(1.4)
Dizziness	9	(2.0)	8	(2.0)	-		-		-		-	
Miscellaneous												
Taste alteration	12	(2.7)	11	(2.5)	1	(0.2)	-		-		-	

[1] Includes those adverse events of unknown relationship to treatment.
[2] Unspecified by the investigators.
[3] Includes "abdominal pain" and "colic abdomen" as coded by the sponsor.
(Source: FDA Reviewer's analysis of NV15182, 48-week Safety Update)

Table 3.1.C. Summary of Treatment-Emergent Adverse Events[1] of at least Moderate Intensity Reported in ≥2% of Patients

Body System/Disorder	Number of Patients	
	n	%
Body as a whole		
Abdominal discomfort	39	(8.8)
Headache	35	(7.9)
Fatigue	30	(6.8)
Abdominal pain	19	(4.3)
Gastrointestinal		
Diarrhea	92	(20.8)
Nausea	46	(10.4)
Dyspepsia	39	(8.8)
Flatulence	26	(5.9)
Vomiting	15	(3.4)
Psychiatric		
Depression	13	(2.9)
Insomnia	11	(2.5)
Dermatological		
Rash	9	(2.0)

[1] Includes adverse events related to treatment, of unknown intensity and/or relationship to treatment.
(Source: FDA Reviewer's analysis of NV15182, 48-week Safety Update)

Reviewer's Comment

The sponsor's Tables of "treatment-emergent" adverse events did not include cases of unknown relationship to treatment or those with unknown severity. The Tables compiled by this reviewer in this addendum report included all these cases.

3.2 Serious or Life-Threatening Adverse Events

A total of 58 patients experienced serious adverse events after 48 weeks. Most of these events (80%) were considered by the sponsor as unrelated to treatment. The treatment-related serious adverse events occurring between weeks 24 and 48 are summarized below.

- Patient 16988/2426, a 43-year-old male, had "frequent bowel movements" (4-5/day) after 6 months of drug treatment. He developed diarrhea, nausea, vomiting, anorexia on day 281 after taking erythromycin. The diarrhea increased in intensity and persisted after erythromycin was discontinued. Due to severe diarrhea, he was hospitalized for 10 days. The diarrhea was considered possibly related to treatment.

- Patient 16989/2381, a 47-year-old male, was hospitalized on day 214 for acute pancreatitis considered possibly related to treatment. At the same time he was also diagnosed to have diabetes mellitus which was thought to be remotely related to treatment.

- Patient 17009/2356, a 53-year-old male, was hospitalized on study day 247 for severe abdominal pain, nausea, vomiting and diarrhea. The abdominal pain was considered by the investigator as remotely related to treatment.

- Patient 17009/2356, a 40-year-old male, had severe flatulence, eructation and abdominal distention on day 122 requiring lead to hospitalization on day 199. The symptoms were considered possibly related to treatment and subsequently resolved.

- Patient 17165/2982, a 28-year-old male, developed severe diarrhea on study day 74 and persisted until day 288. His treatment was discontinued on day 214 due to severe malnutrition. His symptom was considered possibly related to treatment.

- Patient 17193/2864, a 45-year-old male, developed diarrhea of life-threatening intensity on study day 1. He was hospitalized from days 31 to 34, at which time he withdrew from study. The diarrhea was thought to be probably related to treatment.

Reviewer's Comments

1. Diabetes mellitus (patient 16989/3281) and abdominal pain (patient 16993/2267) have been implicated as treatment-emergent adverse events associated with protease inhibitor and saquinavir treatment, respectively. Nevertheless, these adverse events were considered "remotely" related to treatment by the investigators.

2. Patient 17193/2864 was previously reported (week 24 analysis) to have life-threatening diarrhea. However, this case was not accounted for in this 48-week report.

3.3. Adverse Events Associated with Premature Discontinuation of Treatment

According to the sponsor, by week 48, a total of 36 patients withdrew from the study due to clinical adverse events (excluding laboratory toxicity). This represents an additional 12 more patients from the initial 24-week analysis. Table 7 presents data from these additional cases. Adverse events thought to be associated with

and occurring at the time of withdrawal were summarized by this reviewer based on information submitted by the sponsor. For cases in which multiple complaints of the same adverse event were recorded, only the one with the most severe rating is counted. A number of patients experienced multiple adverse events at the time of dropout, with the most frequently reported being diarrhea, nausea and vomiting as shown in this Table 3.3. The majority of these adverse events were rated as moderate to severe intensity. These events were not different from those reported in the 24-week analysis.

Table 3.3. Summary of Adverse Events[1] Associated with Premature Discontinuation of Treatment (Excluding Laboratory Toxicity) from week 24 to week 48

Adverse Events	Number of Patients		
	Severe	Moderate	Mild
	n	n	n
Diarrhea	2	1	2
Nausea	2	2	-
Abdominal pain	1	-	1
Abdominal discomfort	-	1	1
Vomiting	1	3	1
Dyspepsia	1	1	-
Fatigue	-	2	1
Flatulence	1	-	1
Pruritus	-	-	1
Rash	-	1	-
Weight loss	-	-	1

[1] Where more than one similar adverse event was reported by a patient, the one with the most severe rating was recorded.
(Source: FDA Reviewer's analysis of NV15182)

4. Death

The sponsor reported a total of 7 deaths by week 48 of the study. None of these cases were considered by the investigators as related to treatment. Three deaths occurred in the first 24 weeks and 4 in the last 24 weeks. The latter cases are summarized below.

- Patient 16985/2097, a 34-year-old male, was admitted on study day 129 with fever and dyspnea. He was found to have acute renal failure (creatinine of 9 mg/dL), and SQV-SGC was discontinued. His conditioned deteriorated and he died on day 174. The investigator attributed the cause of renal failure to concomitant Vistide treatment for CMV retinitis. The death was not considered treatment-related.

- Patient 17004/2207, a 47-year-old male, was withdrawn from the treatment on day 105 due to insufficient therapeutic response. He had presumptive diagnosis of PCP on day 237 and died of respiratory failure on day 244. The death was considered unrelated to treatment.

- Patient 17048/2244, a 44-year-old male, had history of recurrent cryptococcal meningitis and fungemia with multiple hospitalizations. Study drugs were discontinued due to patient's deteriorated condition on day 329. He died on day 348 with a finding of necrotizing bronchopneumonia. The death was considered unrelated to treatment.

- Patient 17055/2842, a 36-year-old male, was discontinued from treatment due to insufficient virologic response on day 183. He died of lymphoma on day 272 and the death was considered unrelated to treatment.

Reviewer's Comments

1. All these cases of death, with the exception of the first case (16985/2097), can be attributed to known complications of HIV-infection, and not as a direct result of treatment with SQV-SGC.

2. There was one death from acute renal failure reported in this study. The cause of renal failure was thought to be secondary to the use of cidofovir for the treatment of CMV retinitis in this patient. The sponsor was requested to report this case to Gilead Sciences, the manufacturer of cidofovir.

5. Laboratory Findings

5.1. Overviews of Laboratory Abnormalities

According to the sponsor, the data up to date revealed grade 1 toxicities in a number of laboratory parameters; however, only changes indicative of low-grade liver toxicity were considered clinically significant. The number of patients with low-grade AST and ALT elevations remained relatively stable by 48 weeks of treatment.

An overview of abnormal shifts of laboratory tests in patients with normal baselines is presented in Table 5.1.

Table 5.1. Abnormal Shifts of Laboratory Results in Patients with Normal Baseline

Analyte	Percentage[1] of Patients with Grade Shifts			
	0-1	0-2	0-3	0-4
	%	%	%	%
↑ Alkaline phosphatase	6.4	0.9	-	-
↑ AST (SGOT)	21.1	3.6	1.9	1.4
↑ ALT (SGPT)	22.7	5.6	2.9	1.3
↑ Total bilirubin	10.6	1.9	1.4	-
↑ Creatine kinase	25.6	6.7	1.7	2.3
↑ Amylase	12.0	1.6	0.5	-
↑ Glucose	5.0	0.5	-	-
↓ Glucose	10.9	7.3	2.6	3.8
↑ Calcium	2.3		-	0.2
↓ Calcium	4.3	0.5	-	-
↓ Phosphate	8.6	2.2	-	-
↑ Creatinine	5.0	0.5	-	-
↑ Potassium	4.4	2.2	-	-
↓ Potassium	3.2	0.2	-	-
↑ Sodium	4.4	-	0.7	-
↓ Sodium	12.1	0.9	-	-
↓ Hemoglobin	2.1	0.9	-	0.2
↓ Neutrophils	14.8	3.5	1.2	0.3
↓ Platelets	0.9	0.5	0.7	-

[1] Missing data not included in the calculation.
(Source: NV15182, 48-week Safety Update)

5.2. Marked Laboratory Abnormalities

According to the sponsor, the only marked laboratory abnormalities (shifts ≥ grade 3) of clinical significance were AST and ALT elevations. There was no new emergence of any abnormal laboratory toxicity not previously seen in after 24 weeks of treatment. The cumulative incidence of marked laboratory abnormalities by week 48 is presented in Table 5.2.

Table 5.2. Summary of Marked Laboratory Abnormalities

Analyte	Number of Patients with Marked Laboratory Abnormality (N=442)	
	n	(%)
↑AST (SGOT)	14	(3.2)
↑ALT (SGPT)	18	(4.1)
↑ Creatine kinase	18	(4.1)
↑ Amylase	2	(0.5)
↑ Total bilirubin	6	(1.4)
↑ Glucose	4	(0.9)
↓ Glucose	28	(6.3)
↑ Potassium	12	(2.7)
↑ Sodium	3	(0.7)
↓ Neutrophils	6	(1.4)
↓ Platelets	3	(0.7)

(Source: NV15182, 48-week Safety Update)

5.3. Laboratory Abnormalities Associated with Premature Discontinuation of Treatment

Between weeks 24 and 48, there was one additional case in which premature treatment discontinuation was due to laboratory toxicities. The case is summarized below.

- Patient 17187/2886, a 42-year-old man, was withdrawn from the study on day 259 due to grade 4 liver toxicity. A review of laboratory data showed AST and ALT elevations beginning on day 167 to grade 3 levels (272 U/L and 309 U/L, respectively) up until the last data entry on day 287. There was a concurrent mild increase of AP (grade 1) and marked elevation of GGT (grade 4). The patient also had grade 2 hypertriglyceridemia.

6. Pregnancies, Overdosage Exposure

No cases of pregnancies or overdosage exposure have been reported in this study up to this time.

7. Conclusions

A total of 307 patients (69.5%) completed at least 48 weeks of treatment at the time this Safety Update was compiled. There were 139 patients prematurely withdrawn from the study, with the most common reasons being "insufficient therapeutic response" (46.0%), "adverse event/intercurrent illness" (25.9%) and "lost to follow-up" (17.3%). There were 4 additional deaths, all of which were

thought not to be caused by the study drug. Notable among these cases was a patient who died of renal failure attributable to the use of cidofovir for CMV retinitis treatment.

The adverse event profile by week 48 remains similar to that observed at week 24, although some of the previously observed adverse events occurred with increased frequency. The most common adverse events (excluding those considered as "unrelated" to treatment) were diarrhea (38.2%), nausea (24.4%), dyspepsia (20.0%), abdominal discomfort (17.2%), headaches (12.2%), fatigue (12.2%), flatulence (11.8%), abdominal pain (7.9%) and vomiting (6.6%). The majority of these events were of mild to moderate intensity, and no additional cases with life-threatening severity were reported. Diarrhea, nausea, vomiting of moderate to severe intensity were still the most common causes of early withdrawals due to adverse events.

Marked laboratory abnormalities (grade 0 on day 1 to grade 3 or 4, or grade 1 on day 1 to grade 4) were observed with AST, ALT, and CK enzymes in 3 to 4% of patients. Decreased glucose and increased potassium were seen in 6% and 3% of patients, respectively. These figures were not significantly different from those reported in the 24-week analysis. Only one additional patient withdrew from the study due to elevated transaminases (grade 3).

Tables 7.A presents an overview of adverse events of at least moderate intensity in ≥2% of patients at week 24 and week 48. Table 7.B shows comparisons of the frequencies of marked laboratory abnormalities between 24 and 48-week data. Finally, Table 7.C lists the disposition of premature withdrawals for the same time points.

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Table 7.A. Summary of Adverse Events[1] of at least Moderate Intensity in ≥2% of Patients (Week 24 and Week 48 Data)

Body System/Disorder	Number of Patients with Adverse Events of Moderate Intensity or More (N = 442)			
	0 - 24 Weeks		0 - 48 Weeks	
	n	%	n	%
Body as a whole				
Abdominal discomfort	38	(8.6)	39	(8.8)
Headache	33	(7.5)	35	(7.9)
Fatigue	29	(6.6)	30	(6.8)
Abdominal pain	17	(3.8)	19	(4.3)
Gastrointestinal				
Diarrhea	86	(19.5)	92	(20.8)
Nausea	44	(9.9)	46	(10.4)
Dyspepsia	37	(8.4)	39	(8.8)
Flatulence	24	(5.4)	26	(5.9)
Vomiting	13	(2.9)	15	(3.4)
Constipation	9	(2.0)	-	-
Psychiatric				
Depression	-	-	13	(2.9)
Insomnia	9	(2.0)	11	(2.5)
Dermatological				
Rash	9	(2.0)	9	(2.0)

[1] Includes adverse events related to treatment, of unknown intensity and/or relationship to treatment.
(Source: FDA Reviewer's analysis of NV15182)

Table 7.B. Summary of Marked Laboratory Abnormalities (Week 24 and Week 48 Data)

Analyte	Number of Patients with Marked Laboratory Abnormality (N = 442)			
	0 - 24 Weeks		0 - 48 Weeks	
	n	(%)	n	(%)
↑ AST (SGOT)	9	(2.0)	14	(3.2)
↑ ALT (SCPT)	13	(2.9)	18	(4.1)
↑ Creatine kinase	13	(2.9)	18	(4.1)
↑ Amylase	1	(0.2)	2	(0.5)
↑ Total bilirubin	5	(1.1)	6	(1.4)
↑ Glucose	3	(0.7)	4	(0.9)
↓ Glucose	24	(5.4)	28	(6.3)
↑ Potassium	7	(1.6)	12	(2.7)
↑ Sodium	1	(0.2)	3	(0.7)
↓ Neutrophils	2	(0.5)	6	(1.4)
↓ Platelets	1	(0.2)	3	(0.7)

(Source: NV15182)

Table 7.C. Summary of Premature Discontinuations of Treatment (Week 24 and Week 48 Data)

Reason	0 - 24 Weeks		0 - 48 Weeks	
	n	(%)	n	(%)
Insufficient therapeutic response	13	(2.9)	64	(14.5)
Adverse event/intercurrent illness	25	(5.7)	36	(8.1)
Refused treatment/non-cooperation/withdrew consent	13	(2.9)	24	(5.4)
Lost to follow-up	5	(1.1)	8	(1.8)
Laboratory toxicity	3	(0.7)	4	(0.9)
Miscellaneous				
Protocol violation	-	-	1	(0.2)
Death on therapy	1	(0.2)	1	(0.5)
Death off therapy	2	(0.5)	6	(1.4)

(Source: NV15182)

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