CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-659/S-13
20-680/S-11

MEDICAL REVIEW

NDA 20-659 (S-013)
NDA 20-680 (S-011)

DRAFT

Regulatory Review Officer's Review of Supplemental New Drug Applications: 20-659 and 20-680

Date Submitted: **May 22, 1998**
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Date Completed:

Sponsor: Abbott Laboratories
Pharmaceutical Products Division
100 Abbott Park Road
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Drug: Ritonavir capsules and oral solution

Indication: Treatment of HIV Infection

Materials Reviewed:

1.0 RESUME:

Abbott Laboratories submitted a supplemental new drug application in support of traditional approval of ritonavir for patients with less advanced HIV disease. Ritonavir currently has traditional approval for the treatment of patients with advanced HIV disease and accelerated approval for treatment of "less advanced" HIV. The applicant has submitted the following data to support their accelerated approval commitments:

- A final clinical/statistical report for study M94-245: "A Phase III Comparative Trial of Ritonavir Alone, Zidovudine Alone, or the Combination of Ritonavir and Zidovudine In HIV-Infected Patients Without Prior Antiretroviral Therapy" (submitted to IND 43,718, serial 412 dated 2/13/98).

- A final clinical/statistical summary report for study M94-247, "The Safety and Efficacy of Ritonavir plus Current Therapy vs. Placebo plus Current Therapy in HIV-Infected Patients" (IND 43,718, serial 413 dated 2/20/98).

- A final clinical/statistical summary report for study M96-432, "A Phase III Ritonavir Long-Term Trial" (IND 43,718,serial 415 dated 2/26/98).

- A 48-week clinical/statistical summary report for study M96-462, "Safety and Efficacy of Ritonavir in Combination with Saquinavir in HIV-Infected Patients" (IND 43,718, serial 409 dated 1/30/98).

After review of these data, the Division of Antiviral Drug Products (DAVDP) has concluded that the accelerated approval for patients with less advanced HIV-1 disease may be converted to a traditional approval.

2.0 BACKGROUND

On February 29, 1996, Abbott Laboratories presented safety and efficacy data for NORVIR (ritonavir) from studies M94-245 and M94-247 to the Antiviral Drug Products Advisory Committee. Study M94-245 was a surrogate marker study in antiretroviral naïve subjects with CD4 counts greater than 200 cells/mm^3 and Study 247 was a clinical endpoint study in antiretroviral experienced patients with CD4 cell counts less than 100 cells/mm^3. On March 1, 1996, DAVDP approved ritonavir (oral solution and capsules). Based on advice from the committee, the approval consisted of traditional approval for patients with advanced HIV disease and accelerated approval for patients with less advanced HIV disease. The indication in the product labeling reads as follows:

> NORVIR is indicated in combination with nucleoside analogues or as monotherapy for the treatment of HIV infection when therapy is warranted. For patients with advanced HIV disease, this indication is based on the results from a study that showed a reduction in both mortality and AIDS-defining clinical events for patients who received NORVIR. Median duration of follow-up in this study was 6 months. The clinical benefit from NORVIR therapy for longer periods of treatment is unknown.
>
> For patients with less advanced disease, this indication is based on changes in surrogate markers in studies evaluating patients who received NORVIR alone or in combination with other antiretroviral agents.

Recommendations for this dual approval were primarily based on concerns regarding the total duration of safety and efficacy data, approximately 6 months for both studies. Due to rapid enrollment and early detectable differences in clinical outcome between the two treatment arms in study 247, this clinical endpoint study was completed in less than 8 months. The committee was concerned about the appropriateness of extrapolating the clinical benefit seen among patients with advanced HIV disease to those with less advanced HIV. The committee recommended that the sponsor collect longer-term safety and activity data in less advanced patients to support traditional approval for this subgroup. In addition, the division and the committee were concerned about study M94-245's unusual results showing greater surrogate marker improvements among patients receiving ritonavir monotherapy compared to those receiving ritonavir and zidovudine combination therapy.

2.1 BACKGROUND: ACCELERATED APPROVAL COMMITMENTS

In a February 29, 1996 letter to the Division of Antiviral Drug Products, Abbott Laboratories agreed to the following accelerated approval commitments.

1. Provide long-term follow-up safety and clinical endpoint data from ongoing studies M94-245 and M94-247 to assess the comparative clinical efficacy and safety data in patients with advanced stage disease vs. patients with early stage disease.

2. Participate in a clinical study to define the safety and clinical efficacy of ritonavir in pediatric patients.

3. Provide data from a study in patients with higher CD4 cell counts (>100 cells/mm^3) looking for durability of response by evaluating CD4 response, HIV RNA response and safety from a study comparing ritonavir to ritonavir + saquinavir

4. Provide additional clinical data to the Division within 2 years

2.2 BACKGROUND: ACCELERATED APPROVAL COMMITMENT RESPONSES

The following discussion summarizes Abbott Laboratories responses to these commitments.

1. **Provide long term follow-up safety and clinical endpoint data from ongoing studies M94-245 and M94-247 to assess the comparative clinical efficacy and safety data in patients with advanced stage disease vs. patients with early stage disease.**

   The applicant submitted final study reports for M94-245, M94-247 and M96-432. Please refer to sections 3.1, 3.2, and 3.3, respectively, for review of the long-term safety data from these trials.

2. **Participate in a clinical study to define the safety and clinical efficacy of ritonavir in pediatric patients.**

   On January 21, 1997, Abbott Laboratories submitted an NDA supplement that contained pharmacokinetic, safety and preliminary activity data from study M95-310. This was a multi-center, open-label, dose-escalation study of four dosing levels (ranging from 250-400 mg/m^2) of ritonavir in children aged 6 months to 18 years. Only 4 patients were enrolled under the age of two years; therefore, the data presented in this supplement were only analyzed for the older than two age group. A dose of approximately 400 mg/m^2 appeared to yield ritonavir concentrations similar to that of the recommended adult dose of 600 mg bid. There was no clear dose response for activity as measured by changes in CD4

and plasma HIV RNA; however, all dosing levels appeared to produce substantial changes from baseline for these markers. The toxicity profile of ritonavir in pediatric patients appeared to be similar to that observed in adults. Therefore, on March 14, 1997, the division took an approval action on this pediatric use supplement. The package insert was modified to include a description of pharmacokinetic and safety data and recommendations for dosing in children greater than two years of age.

3. Provide data from a study in patients with higher CD4 cell counts (>100 cells/mm^3) looking for durability of response by evaluating CD4 response, HIV RNA response and safety from a study comparing ritonavir to ritonavir + saquinavir

Abbott Laboratories conducted a safety and activity study of four different dosing combinations of ritonavir and saquinavir. Results from this study (M96-462) have been submitted and reviewed (see section 3.4 for details). Originally the applicant had planned to enroll patients in a larger comparative trial of ritonavir + saquinavir after completing this study. Abbott Laboratories has stated that no larger trials for this combination is planned. However, Abbott may obtain data from an ongoing Danish study which compares ritonavir plus two nucleoside analogues to indinavir plus two nucleoside analogues to ritonavir/saquinavir plus two nucleoside analogues.

3.0 CLINICAL TRIALS

3.1 Study M94-245

"A Phase III Comparative Trial of Ritonavir Alone, Zidovudine Alone, or the Combination of Ritonavir and Zidovudine in HIV-Infected Patients without Prior Antiretroviral Therapy"

This study was reviewed for original NDAs 20-659 and 20-680 (ritonavir oral solution and capsules, respectively). The reader may refer to the medical officer's review dated May 24, 1996, for a detailed description of the protocol and study results. The following discussion will highlight new information from longer-term follow-up of patients participating in study M94-45. This summary will also address information pertinent to Abbott's proposed changes for the NORVIR package insert.

3.1.1 Protocol

3.1.1.1 Study Design and Patient Population

Study 245 was a randomized, double blind, three-arm, "surrogate-marker" study in 356 HIV-infected adults. Patients were randomized to one of the three following treatment arms:

1) zidovudine 200 mg tid + ritonavir placebo
2) ritonavir 600 mg bid + zidovudine placebo
3) zidovudine 200 mg tid + ritonavir 600 mg bid

This study had statistical power to detect differences in mean changes from baseline over time in HIV RNA levels and CD4 cell counts.

To be eligible for randomization patients were required to be treatment naive with a CD4 count of at least 200 cells/mm^3 and at least one screening HIV RNA level of at least 15,000 copies/mL.

Per protocol amendment #4, patients were to continue taking double-blind study drug for at least 8 months unless they fulfilled one of several criteria to switch to open-label ritonavir. These criteria included: clinical disease progression, a 50% decrease from baseline in absolute CD4 cell counts, or recurrence of drug toxicity subsequent to dose reduction.

3.1.2. Results

3.1.2.1 Efficacy

In the original NDA, mean changes in HIV RNA levels and CD4 cell counts over 16 weeks were analyzed. Additional data out to 24 weeks was available at the time of

the advisory committee. For this supplement, analyses of changes in HIV RNA and CD4 counts over 48 weeks were submitted (see Table 3.1.2.1-A). The overall results of these analyses were similar to that of the 16-week analyses: ritonavir monotherapy produced larger decreases in HIV RNA and larger increases in CD4 cell counts than zidovudine monotherapy. Also, as was observed in 16-week analyses, ritonavir monotherapy produced larger decreases in HIV RNA and larger increases in CD4 cell counts over 48 weeks than the combination regimen. At the time of the original NDA, this unusual result was not fully explained. The hypothesis was that the poorer performance of the combination regimen was due to problems with tolerability of this regimen as administered in this study and not a result of virologic or pharmacologic antagonism between the two drugs. Several lines of evidence supported this hypothesis, including the high discontinuation rate for the combination regimen, lack of virologic antagonism in *in vitro* studies, and lack of a pharmacologic effect of zidovudine on ritonavir in pharmacokinetic drug interaction studies.

Table 3.1.2.1-A. Average Mean Changes from Baseline in HIV RNA and CD4: Abbott's Analyses of Study 245

	HIV RNA (log_{10}) Mean of Average Change from Baseline Over 48 weeks	CD4 Mean of Average Change from Baseline Over 48 weeks
Combination	-0.92	40
Ritonavir	-1.02	77
ZDV	-0.49	2

Source: IND 43,718; SN 412; Vol. 1: Tables 28 and 30

Additional data (shown in table 3.1.2.1-B) included in this study report showed that mean ritonavir trough concentrations among patients receiving the combination regimen were substantially lower than those observed among patients receiving ritonavir monotherapy. Since a previous pharmacokinetic study has shown that ZDV does not decrease ritonavir levels during direct observed therapy, these results suggest that nonadherence with the poorly tolerated combination regimen was responsible for the decrease in ritonavir concentrations. Ritonavir trough concentrations for those on the combination were nearly half that of those receiving monotherapy. These results offer further evidence against possible virologic antagonism. In addition, studies evaluating ritonavir as part of triple combination therapy with either, ZDV and ddC, or ZDV and 3TC, have shown expected reductions in plasma HIV RNA. In these studies, ritonavir was dose escalated for 2 weeks prior to the addition of nucleoside analogues. This apparently improves the initial tolerability of the combination of ritonavir and zidovudine, drugs that produce similar gastrointestinal intolerance during dose initiation.

Table 3.1.2.1-B. Summary of plasma ritonavir trough concentrations

Week	Ritonavir Monotherapy		Combination Therapy		Ratio*	p-value
	n	Mean #	n	Mean #		
4	83	2.2	64	1.7	0.8	0.225
8	79	2.4	60	1.2	0.5	0.005
12	78	2.0	52	1.2	0.6	0.042
16	73	1.7	48	0.8	0.5	0.016

As calculated by the sponsor using back-transformed mean
* Combination vs. monotherapy
Source: Table 44, IND 43,718, SN 412, Vol. 108.1, p.163.

Although ritonavir appeared to produce greater plasma HIV RNA reductions than ZDV throughout the duration of the study, there was a substantial amount of missing data by 48 weeks. This was due to a large number of treatment discontinuations, many of which were related to the poor tolerability of ritonavir oral solution. The reduction in the number of patients with assessments at 48 weeks precludes the presentation of this longer-term data in the package insert. The percentages of patients with HIV RNA measurements at 16, 24, 32 and 48 weeks are shown in the following table. A higher percentage of patients had CD4 measurements as compared to HIV RNA measurements at 48 weeks. For the ritonavir arm, 53% of patients had CD4 measurements and 38% had HIV RNA measurements at 48 weeks.

TABLE 3.1.2.1-C. Number (percentage) of Patients with HIV RNA Measurements

	Combination	Ritonavir	Zidovudine
Number randomized	116	118	121
Week 16	59 (51%)	80 (68%)	82 (68%)
Week 24	46 (40)	69 (58)	73 (60%)
Week 32	50 (43%)	62 (53%)	74 (62%)
Week 48	32 (28%)	45 (38%)	52 (43%)

3.1.2.2 Safety

Patients who completed the double-blind phase of the study or met other criteria as specified in section 3.1.1.1 of this review were able to enter the open-label portion of the study. Although only half of the patients randomized completed the double-blind phase of the study, all patients who completed the double-blind portion of the study completed at least 48 weeks of therapy. A similar number of patients initially randomized to ZDV or ritonavir monotherapy discontinued the study prematurely. Most treatment discontinuations were due to adverse events. There was more

treatment discontinuations due to adverse events on ritonavir-containing arms. The number of patients withdrawing from the study is shown in table 3.1.2.2-A.

Table 3.1.2.2-A. Study 245: Patient Disposition

	Combination	Ritonavir	Zidovudine
RANDOMIZED	117	118	121
Entered Double Blind	116	117	119
Discontinued Study	77 (66%)	56 (48%)	55 (45%)
Abbott termination	9	13	13
Adverse Event	49 (42%)	36 (31%)	22 (18%)
Admission Criteria	0	0	1
Personal Reasons	8	4	9
Lost to Follow-up	8	2	7
Required prohibited medication	0	0	1
Other	3	1	2
Entered open-label phase	39	61	64

3.1.2.2.1 Clinical Adverse Events

No study patient died during the double-blind treatment period or during long-term ritonavir exposure. As in the earlier report, there was a high frequency of adverse events associated with the use of ritonavir, particularly for the combination regimen. The most frequently reported ritonavir-associated adverse events involved the gastrointestinal and neurologic body systems with nausea, vomiting, diarrhea, and various paresthesias being the most common. In the final study report, events that were more common among patients receiving ritonavir compared to those receiving ZDV included: diarrhea, circumoral paresthesia, paresthesia, peripheral paresthesia, tremor, vasodilatation, hypertension and herpes simplex. All of the above events, except for hypertension, herpes simplex, and tremor were also more common among patients receiving combination therapy than among those receiving zidovudine monotherapy. All of these events were of similar (but slightly greater) frequency than those listed in the earlier report except for hypertension and herpes simplex infections. These two adverse events will be discussed in greater detail below.

Hypertension

Three (2.6%), 12 (10.3%), and 3 (2.5%) patients were reported to have treatment-emergent hypertension on the combination, ritonavir and zidovudine arms, respectively. Although the adverse event coded "hypertension" was more frequent among patients randomized to ritonavir than among those randomized to zidovudine, it was not more frequent among patients receiving combination therapy. In addition, treatment groups did not differ with respect to mean changes in systolic and diastolic blood pressure. The number of patients who had an abnormally high systolic blood pressure (> 40 mm increase or > 180 mm with a rise of at least 20mm) at any time during treatment was 5 (4.4%), 0, and 0 for the combination, ritonavir, and zidovudine groups, respectively. The number (%) of patients who had an abnormally high diastolic blood pressure (>25 mm increase or > 120mm with an increase of 20mm) at

any time during treatment was 3 (2.6%), 4 (3.5%) and 1 (0.8%) for the combination, ritonavir, and zidovudine groups, respectively. In conclusion, there did not appear to be a consistent trend that demonstrated an adverse effect of ritonavir on blood pressure measurements.

Herpes Simplex

The differences observed in the frequency of this event may have depended on how these events were reported. The percentages of patients with a medical history of HSV at baseline were similar among treatment groups. During treatment, when HSV was classified as an adverse event there were more cases among patients receiving ritonavir. When herpes simplex infections were classified as an HIV-related event, there were numerically more cases among patients receiving zidovudine. When counting the total number of patients with HSV episodes, classified as either HIV-related or treatment emergent, the number of patients with HSV episodes on the ritonavir and ZDV treatment arms were similar as shown in table 3.1.2.2.1-A.

Table 3.1.2.2.1-A. The number (percentage) of patients with HSV infections.

	Combination	Ritonavir	Zidovudine
Medical History of HSV	(20)	(15)	(17)
Classified as HIV-Related Events	4 (3.4)	4 (3.4)	10 (8.4)
Classified as Adverse Events	4 (3.4)	12 (10.3)	2 (1.7)
Total	8	16	12

Other Clinical Adverse Events of Interest

There were no cases of clinical pancreatitis in study 245.

3.1.2.2.2 Laboratory Adverse Events

Hematology

Ritonavir appeared to produce generally favorable effects on hematologic parameters compared to ZDV.

Chemistry

In the applicant's analyses, mean changes from baseline at the final double-blind visit were reported for chemistry laboratory values. Among these analyses, only cholesterol and triglycerides measurements showed substantial and clinically significant perturbations when assessed using mean changes from baseline. Fasting samples were used in these analyses. Mean changes from baseline in these laboratory measurements are shown below in table 3.1.2.2.2-A.

Table 3.1.2.2.2-A. Cholesterol and Triglycerides: Mean Changes from Baseline at Final Visit

	Combination	Ritonavir	Zidovudine
Cholesterol (mg/dL)	+12	+29	0
Triglycerides (mg/dL)	+72	+149	+26

Source: IND 43,718 SN 412, page209, Table 58.

The sponsor also analyzed laboratory abnormalities by evaluating the percentage of patients exceeding defined "extreme" values (Table 3.1.2.2.2-B). Abbott states "With the exception of SGOT/AST, SGPT/ALT, GGT, and CPK, the number of patients experiencing chemistry values exceeding an extreme upper limit was relatively small and equally distributed among randomization groups." However, Abbott's definitions for extreme values for some chemistry laboratory parameters were higher than many clinicians would use in managing patients. For example, extreme levels for cholesterol and triglycerides were 500 mg/dL and 1500 mg/dL, respectively. It seems likely that many physicians would classify lesser increases as "extreme" and as requiring intervention. In choosing protocol criteria for extreme levels of lipids, Abbott's original intention was to reduce mandatory drug discontinuation/interruption for study patients experiencing asymptomatic laboratory abnormalities. At the time these trials were being conducted, there were few potent treatments for HIV and investigators were willing to accept higher levels of asymptomatic laboratory abnormalities in patients achieving a good antiviral response. Presently, given the availability of more treatment options and long-term use of antiretroviral therapy, lesser degrees of lipid abnormalities are of concern and should be included in the package insert.

In the sponsor's original analyses of lipid abnormalities, no patient had a cholesterol level greater than 500 mg/dL. We asked Abbott to re-analyze these data using lesser degrees of cholesterol elevations (> 240 mg/dL and > 300 mg/dL). These data are shown in table 3.1.2.2.2-B. More than one-fourth of the patients receiving ritonavir monotherapy had cholesterol elevations exceeding levels considered a threshold for treatment.

Table 3.1.2.2.2-B. Number (%) of Patients with Extreme Values of Selected Chemistry Parameters

Chemistry Variable	Extreme Value	Combination	Ritonavir	Zidovudine
Glucose	> 250 mg/dL	3 (2.6)	1 (0.9)	1 (0.9)
AST	> 180 (IU/L)	6 (5.3)	11 (9.5)	3 (2.5)
ALT	> 215 (IU/L)	6 (5.3)	9 (7.8)	4 (3.4)
GGT	> 300 (IU/L)	2 (1.8)	6 (5.2)	2 (1.7)
CPK	>1000 (IU/L)	11 (9.6)	14 (12.1)	13 (11.0)
Triglycerides *	>1500 mg/dL > 800 mg/dL	2 (1.8) 11 (9.6)	3 (2.6) 20 (17.2)	0 5 (4.2)
Cholesterol	> 300 mg/dL > 240 mg/dL	8 (6.9) 18 (15.5)	12 (10.3) 31 (26.5)	0 6 (5)

Source: Excerpted from IND 43,718, Serial 412, Tables 61 and 64.
Only fasting samples used (at least eight hours) for triglycerides.

Glucose

After the approval of four protease inhibitors, post-marketing reports of hyperglycemia or exacerbation of hyperglycemia among patients with diabetes mellitus came to FDA's attention. In retrospect, all patients in study 245 with an extreme glucose value had elevated glucose levels at baseline. During treatment, elevated levels in these patients were similar to that observed at baseline.

Creatinine

After approval of ritonavir, there were publications documenting increases in serum creatinine associated with the use of ritonavir; some of these reports involved cases of dechallenge/rechallenge. This information is included in the current package insert. No patient had renal insufficiency or an "extreme" level (>3.6 mg/dL) of creatinine in study 245.

Myocardial Infarction

There were no cases of myocardial infarction in study 245.

3.1.2.3. Conclusions

In study 245, the greater reductions in HIV RNA and increases in CD4 cell counts produced by ritonavir as compared to zidovudine over the first 16 weeks of treatment appeared to persist out to 48 weeks. However, a substantial amount of discontinuations and missing data past 24 weeks precludes this information from being presented in the package insert. The poorer performance of the ritonavir/zidovudine combination appears to be related to nonadherence to the poorly tolerated regimen. This is supported by pharmacokinetic data. This is also supported by laboratory data that suggest diminished ritonavir-associated lipid abnormalities for the combination therapy compared to ritonavir monotherapy.

The safety profile of ritonavir was well characterized during the first 16 weeks of study, with gastrointestinal intolerance and paresthesias predominating. No new adverse events appeared with longer-term follow up in study 245. In this report, herpes simplex infections and hypertension were listed as adverse events occurring with a greater frequency among patients receiving ritonavir; however, when looking at both HIV-related events and adverse events and specific blood pressure measurements, respectively, no compelling trends for these adverse events were observed.

Current guidelines for antiretroviral treatment, which recommend prolonged and early treatment necessitate a closer scrutiny of the lipid abnormalities associated with ritonavir. As such, analyses using different cut-offs for "marked" triglyceride and cholesterol levels have been conducted and will be updated in the package insert.

The updated safety data showed that ritonavir may cause increases in transaminases in approximately 7-8%. This is slightly greater than that reported previously.

3.2 Study M94-247

"The Safety and Efficacy of Ritonavir plus Current Therapy vs. Placebo plus Current Therapy in HIV-Infected Patients"

This study was reviewed for original NDAs 20-659 and 20-680 (ritonavir oral solution and capsules, respectively). The reader may refer to the medical officer's review dated May 26, 1996, for a more complete description of the study protocol and results. The following will highlight new information from longer-term follow-up of patients participating in study 247. This summary will also focus on information pertinent to Abbott's proposed changes for the Norvir package insert.

3.2.1 Protocol

3.2.1.1 Study Design and Patient Population

Study 247 was a double-blind, randomized, two-armed, parallel, multi-center, international clinical trial designed to compare ritonavir 600 mg bid with placebo added to existing nucleoside therapy (if any) in HIV-infected patients with CD4 cell counts ≤ 100 cells/mm^3. All patients were required to have had at least 9 months of prior antiretroviral therapy. The study was designed to detect differences in clinical endpoints, defined as the development of a new AIDS-defining event or death. The first 150 patients with HIV RNA levels >15,000 copies/mL were to be assessed for antiviral activity by plasma HIV RNA measurements during the first 16 weeks of study. Subsequent samples were also analyzed. Of note, for a discussion that follows, patients with screening triglyceride levels exceeding 400 mg/dL were excluded from participation.

3.2.2. Results

3.2.2.1 Patient Disposition and Demographics

A total of 1090 patients were randomized, 543 to ritonavir and 547 to placebo. Two patients in each arm were dispensed drug/placebo but did not initiate treatment. The double-blind portion of the study was closed on Dec. 15, 1995, approximately one week after the protocol-specified number of clinical events was achieved. Patients who experienced an AIDS-defining event during the double-blind portion of the study were eligible to receive open-label treatment with ritonavir after the first 16 weeks of treatment. Those who completed the protocol were eligible for open-label treatment on Jan. 8, 1996, after study closure. Patient disposition is shown in table 3.2.2.1-A.

Table 3.2.2.1-A. Study 247: Patient Disposition

	Ritonavir	Placebo
Randomized	543	547
Entered Double-blind	541	545
Died	58	80
Prematurely Terminated Double Blind Portion	92	34
Lost to follow-up	23	6
Entered Open Label	391	431
Died	28	47
Prematurely terminated open label portion	114	111
Lost to follow-up	16	23

Demographic Characteristics

Demographic characteristics were covered in the initial review. Treatment arms appeared to be balanced.

Study Duration/Duration of exposure

Through the double-blind period the median duration of follow-up was 31 weeks for the ritonavir group and 29 weeks for the placebo group. The median duration of follow-up through the entire study period was 51 weeks for patients randomized to either group.

Median durations of exposure to ritonavir and placebo are listed in table 3.2.2.1-B for the double-blind and open-label periods of the protocol. Median duration of ritonavir exposure approached one year. Those who were initially randomized to placebo but then switched to ritonavir in the open-label period had a median duration of ritonavir exposure of approximately 5 months.

Table 3.2.2.1-B. Study 247: Median Duration of Exposure to Study Drug

	Ritonavir	Placebo
Double blind	180 days (24 weeks)	181 days (24 weeks)
Through Open label Period	286 days (41 weeks)	146 days (21 weeks)

#Exposure to ritonavir

3.2.2.2 Efficacy

An analysis of "time to development of an AIDS-defining event or death" was completed for the double-blind period. The number of clinical events in the sponsor's updated analysis differs slightly from that presented in the current package insert. This is due to slightly longer follow-up (approximately 3 weeks) in the final report. Specifically, according to protocol amendment #3, the double-blind phase of the study was to terminate when 191 patients either died or experienced documented AIDS-defining events.[1] This pre-specified number of events was reached on December 15, 1995. An analysis of all the events up to that time point supported the initial approval of ritonavir and is included in the current package insert. Based on that analysis, all investigative sites were notified that the double-blind period of the study was to end on Jan. 8, 1996. All patients were eligible to transfer to the open-label phase of study 247 as of that date. Thus, the analysis in the final report includes follow-up as of Jan. 8, 1996. Compared to the previous analysis, the number of events was increased in both arms, but the overall conclusions remain the same: treatment with ritonavir was associated with decreases in AIDS-defining event and mortality rates as compared to placebo. Since the documentation procedure for AIDS-defining events changed after Jan. 8, 1996, analyses of disease progression was conducted only for the double-blind period. However, deaths that occurred at any time during the conduct of the double-blind and open-label periods of this study have been included in an analysis of patient survival. Notably, the difference in mortality is apparent even after treatment switchovers during the open-label phase (see table 3.2.2.2-A).

TABLE 3.2.2.2-A. STUDY 247: DEATHS DURING STUDY PERIODS

	Ritonavir	Placebo
Double Blind Period	59	80
Open-Label Phase	28	47
Total Study duration	87	127

Source: IND 43,718, serial 413.

3.2.2.3. Safety Outcomes

3.2.2.3.1 Clinical Adverse Events

Similar to study 245, the most frequently reported adverse events for study 247 involved the digestive and nervous systems and body as a whole. The adverse events that were significantly greater among patients randomized to ritonavir, as compared to placebo, were similar to the earlier report; however, urticaria was noted to occur with an increased frequency in this report (7 cases, ritonavir vs. 1 case, placebo). Based on post-marketing reports, the potential for anaphylactoid reactions is currently listed in the Warning section of the package insert.

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1 The protocol specified number was to include all those events occurring beyond the first four weeks of study; however, in the primary analysis all events were counted, including those occurring within the first four weeks of the study.

According to Abbott's final study report, the percentages of patients discontinuing treatment due to adverse events were 21% among those randomized to ritonavir compared to 8.3% for those receiving placebo. This was similar to that reported in the safety update for the original NDA. The most common reasons for discontinuation were due to GI complaints.

There were a greater number of serious adverse events in the placebo arm, probably related to progression of HIV. The number and type of adverse events were similar to those previously reported.

3.2.2.3.2 Laboratory Adverse Events

As in the previous report, ritonavir had a generally favorable effect on hematologic parameters, with more patients randomized to placebo experiencing extremely low hematologic values. However, ritonavir was associated with significant elevations in chemistry labs including triglycerides, cholesterol, SGPT, uric acid, and CPK. In addition, a greater number of patients receiving ritonavir developed hyperbilirubinemia. This was similar to that reported in the original NDA, safety update. The percentages of patients with abnormal lipid profiles are shown in table 3.2.2.3.2. As stated above for study 245, FDA asked Abbott to determine the frequency of lesser degrees of triglyceride and cholesterol elevations. Using a cholesterol level of 500 mg/dL is not discriminating; no patient had levels exceeding this amount. Lesser cholesterol elevations are certainly in the range where therapeutic intervention may be indicated.

Table 3.2.2.3.2. Study 247: Number (Percent) of Patients with Extreme Values of Triglycerides or Cholesterol.

Lab	Extreme Value	Ritonavir	Placebo
Triglycerides	>1500 mg/dL	28 (9.9)	1 (0.3)
	> 800 mg/dL	178 (33.5)	51 (9.4)
Cholesterol	> 500 mg/dL	0	0
	> 300 mg/dL	48 (8.9)	0
	> 240 mg/dL	97 (17.9)	12 (2.2)

3.2.2.3.3 Additional Analyses of Clinical and Laboratory Adverse Events

Subgroup Analyses

Abbott performed safety analyses stratified by subgroups for certain COSTART terms of interest. Subgroups included: baseline demographic factors, medical conditions, and concurrent medication usage. COSTART terms of interest included: allergic reactions, bleeding events, hepatic events, hyperglycemia/diabetes mellitus, hypertriglyceridemia, hypotension, myocardial infarction/cardiac events, pancreatitis/increased amylase, renal events, seizures and syncope/loss of consciousness. Most of these events of interest were those FDA recognized as potential concerns after reviewing the first quarterly periodic reports. For each of these analyses, Abbott evaluated differences in attributable risks. For these subgroup

analyses, Abbott reports that clinically and statistically significant associations were found for age and treatment-emergent hypertriglyceridemia and for weight and treatment-emergent hepatic events.

During the double-blind period, older patients (>35 yrs.) who received ritonavir had a higher frequency of hypertriglyceridemia than younger patients. This relationship was not seen when total ritonavir experience (open-label phase) was considered. During the double-blind period, the incidence of all hepatic events, particularly abnormal LFTs, was greater among patients who weighed less than 140 pounds compared to those weighing more. This relationship was also observed in the open-label phase. The association between weight and hepatic events may have been influenced by an increase in events among higher weight patients receiving placebo rather than an increase in hepatic events among lower weight patients receiving ritonavir (See table 3.2.2.3.1). Pharmacokinetic studies in adults have demonstrated that ritonavir concentrations are independent of body weight.

Abbott also conducted subgroup analyses for selected chemistry laboratories, including glucose, creatinine, hepatic transaminases, cholesterol, triglycerides, amylase, and creatinine. There appeared to be an association between elevation in triglycerides and baseline triglyceride levels. There was a larger number of patients experiencing extreme (> 800 mg/dL) triglyceride levels among patients with baseline levels greater than 400 mg/dl than among those with baseline levels less than 400 mg/dL. Likewise, there were a larger number of individuals with extreme triglyceride levels and extreme ALT/AST levels among patients with abnormal transaminases (> 5 X ULN) at baseline. See Table 3.2.2.3.1.

Table 3.2.2.3.1. Attributable Risks for Adverse Clinical/Laboratory Events, Subgroup Analyses.

Event/Strata	Ritonavir	Placebo	Difference in Attributable Risks
Hypertriglyceridemia (>1500 mg/dL)			
>35 years	9.9%	0.3%	7%*
≤35 years	4.2%	1.5%	
Hypertriglyceridemia (>800 mg/dL)			
>35 years	36.2	11.9	1.3%
≤35 years	28.9	5.9	
>400 mg/dL at baseline	70.6%	40.8%	8.2%*
≤400 mg/dL at baseline	26.5%	4.9%	
Hx of Hepatic disorder	33.7%	17.8%	9.7%*
No Hx of hepatic disorder	33.6%	8.0%	
Hepatic events (clinical and laboratory events combined)			
> 140 lbs.	8.1%	6.5%	8%*
≤ 140 lbs	12.8%	3.5%	
ALT > 5 times the upper limit of normal			
Hx of Hepatic disorder	18.9%	6.7%	10.7%*
No Hx of hepatic disorder	6.2%	4.7%	

*Statistically significant
Source: IND 43,718, serial 413, Statistical tables 75

Hypertension
A possible increase in the frequency of hypertension was reported among patients receiving ritonavir monotherapy in study 245. In study 247, a similar number (%) of patients 9 (1.7%) and 14 (2.6%) receiving placebo and ritonavir, respectively, were reported to have hypertension.

Herpes Simplex
A possible increase in the number of herpes simplex infections was noted among patients receiving ritonavir monotherapy in study 245. A similar number of patients among the two treatment arms had herpes simplex infections listed as treatment-emergent adverse events in study 247: ritonavir 25 (4.6%), placebo 20 (3.7%).

Creatinine
One patient receiving ritonavir and two receiving placebo had creatinine levels exceeding Abbott's "extreme" criterion (>3.6 mg/dL).

Myocardial Infarction
For the whole study duration, one individual experienced a myocardial infarction. This occurred in a patient originally randomized to ritonavir. It would be difficult to formulate conclusions based on one event.

Pancreatitis

There were 23 cases of pancreatitis throughout the entire study period. FDA requested case narratives for review. Seven of these 23 cases occurred among patients receiving placebo or during the study lead-in phase. Thus, sixteen cases (1.6%) occurred among 974 patients receiving double-blind or open-label ritonavir throughout the total study period. Three of the sixteen cases of pancreatitis that occurred among patients receiving ritonavir (double-blind or open-label) had TG levels greater than 800 mg/dL. One of these cases occurred after ritonavir had been discontinued for two months (this case was discussed in the original review). Several of the remaining cases had possible alternate risk factors including the use of ddI (1) or conditions such as CMV (4), MAI (1), cryptosporidiosis (1), cholangitis (1) or sepsis (1). However, the presence of potential alternative etiologies does not rule out the possibility of a causal association with ritonavir.

In this study, the overall frequency of pancreatitis was relatively low and appeared to be less than that reported for didanosine (range 1-7%, adult studies, 3% pediatric studies); however, since ritonavir is known to cause substantial increases in triglycerides, a plausible causal mechanism for ritonavir-induced pancreatitis exists.

3.2.3. Conclusions

Additional follow-up from study 247 confirmed the clinical benefit of ritonavir, particularly with respect to mortality. A decrease in mortality rate was observed between the two treatment arms even after switchovers were allowed, suggesting a benefit to an earlier intervention with ritonavir in these advanced patients.

The adverse event profile observed with longer-term follow-up was similar to that of the earlier report. This is not surprising since the majority of ritonavir-related adverse events usually occur early in the initiation of treatment. However, clinical data to evaluate the occurrence of fat redistribution, which may occur with prolonged treatment, were not systematically collected.

According to subgroup analyses conducted by Abbott, hepatic adverse events seemed to occur with greater frequency among patients with lower weight (< 140 lbs.) and also among those with elevated transaminases at baseline. In addition, hypertriglyceridemia appeared to occur more frequently among patients with triglyceride levels > 400 mg/dL at baseline and among those with elevated transaminases at baseline. Thus, physicians may need to be more cautious when using ritonavir in patients with abnormal lipid profiles and elevated hepatic transaminases. Low weight may be a marker for more severe underlying disease. Physicians should also take this factor into consideration.

The frequency of pancreatitis was relatively low, less than that reported for ddI, and did not appear to be out of range of that reported for other antiretrovirals (approximately 1%). However, since ritonavir can cause profound increases in triglycerides, particularly in those patients with elevated levels at baseline, a potential

causal mechanism for pancreatitis exists. Cautionary statements to this effect should be reinforced in the package insert.

3.3 Study M96-432

3.3.1. Study Title

"A Phase III Ritonavir Long-Term Trial"

3.3.2. Objectives:

The objectives of this study were to evaluate longer-term safety and efficacy of ritonavir 600 mg BID (or at a dose as agreed by an investigator and Abbott physician).

3.3.3 Study Design

Study M96-432 was an open-label, multicenter, multicountry trial in HIV-infected patients who were participating in ritonavir studies M93-134X, M94-169, M94-229, M94-245, M94-247, M95-320 or had participated in studies M92-848, M93-030, M93-107, M93-052, M93-112 or M92-773. In addition, patients who had previously discontinued ritonavir therapy or had not been allowed to participate in a long-term extension period had the opportunity to resume ritonavir therapy. Patients who received ritonavir in the expanded access program were not eligible to participate in this study.

Patients who did not directly rollover to this study from a previous study were followed every two weeks for four weeks, at a 12-week visit, and then followed every 12 weeks thereafter. Patients who participated in previous ritonavir studies were followed every 12 weeks.

3.3.4. Analytical and Statistical Plans

3.3.4.1. Efficacy

Statistical tests were performed in the analysis of patient survival only.

3.3.4.2 Safety

Proportions of patients with treatment-emergent adverse events were summarized according to severity and causality. Adverse events that resulted in premature discontinuation from study drug were also summarized for each treatment arm. Laboratory abnormalities (hematology, clinical chemistry and baseline urinalysis) were graded using ACTG criteria.

3.3.7. Results

3.3.7.1. Patient Disposition

A total of 818 patients were enrolled into this study. Table 3.3.7.1.A. describes the number of patients evaluable for safety and efficacy by study and duration of exposure.

Table 3.3.7.1.A. Study 432: Duration of Ritonavir Exposure.

Study of Original Enrollment	Duration of Exposure in Weeks (n=817)*			
	0-12	12-18	18-24	>24
M92-773 (n=4)	3	1	0	0
M92-848 (n=18)	18	0	0	0
M93-030 (n=8)	8	0	0	0
M93-052 (n=3)	2	1	0	0
M93-107 (n=15)	15	0	0	0
M93-112** (n=26)	9	5	1	11
M93-134*** (n=17)	0	1	0	16
M94-229 (n=11)	2	0	2	7
M94-245 (n=203)	37*****	76	21	69
M94-247 (n=506)	123#	203##	132	48
M94-251 (n=3)	1	2	0	0
M95-320 (n=3)	0	3	0	0
Total	218	292	156	151

Source IND 43718 serial 415 vol 1 table 4
*one patient was a screening failure in M93-030, but enrolled in M96-432
** Includes patients from M94-169
***Includes patients from M93-134X
*****8 of 37 patients did not take ritonavir in M96-432
#38 of 123 patients did not take ritonavir in M96-432
##1 of 203 patients did not take ritonavir in M96-432

3.3.7.1.1. Reasons for Premature Discontinuation

Eighty-nine (10.9%) patients enrolled into this study prematurely discontinued due to an adverse event or HIV-related event. Table 3.3.7.1.1.A. summarizes the reasons for premature discontinuations.

Table 3.3.7.1.1-A. Reasons for Premature Discontinuation

	Duration of Ritonavir Exposure				
Reason for Discontinuation	**0-12 Months (n=219)**	**>12-18 Months (n=292)**	**>18-24 Months (n=156)**	**> 24 Months (n=151)**	**Overall (n=818)**
AE or HIV-related event	57 (26%)	24 (8.2%)	5 (3.2%)	3 (2%)	89 (10.9%)
Concurrent Condition	2 (0.9%)	3 (1%)	2 (1.3%)	1 (0.7%)	8 (1%)
Death	8 (3.7%)	6 (2.1%)	1 (0.6%)	1 (0.7%)	16* (2%)
Lost to follow-up	12 (5.5%)	14 (4.8%)	7 (4.5%)	6 (4%)	39 (4.8%)
Other**	54 (24.7%)	31 (10.6%)	19 (12.2%)	5 (3.3%)	109 (13.3%)
Personal Reasons	24 (11%)	35 (12%)	13 (8.3%)	7 (4.6%)	79 (9.7%)
Required Prohibited Meds	13 (5.9%)	13 (4.5%)	17 (10.9%)	1 (0.7%)	44 (5.4%)

Source IND 43718 serial 415 vol 1 table 10
*16 pts died > 30 days post treatment, 2 pts dies during the study, but never received ritonavir
**Includes switching to different meds, increasing viral load, primary MD changing med, entering different study, decreasing CD4 and withdrew consent

3.3.7.2. Demographic Data

The mean age of the patients enrolled into the study was 39.1 years (range: 20-68 years). The study population was predominantly conducted in white (86%) males (92%).

3.3.7.3. Efficacy Outcomes

3.3.7.3.1. Survival

A total of 99 (18.2%) patients who were randomized to ritonavir in study M94-247 and 142 (26%) patients originally randomized to placebo in study M94-247 had died. The applicant reports that the estimated hazard ratio is 0.694, with a 95% confidence interval of 0.537 to 0.897. The applicant states that these results represent a statistically significant reduction in mortality of 30.6% for the ritonavir group compared to the placebo group in study M94-247. Table 3.3.7.3.1-A summarizes the risk of mortality for M94-247 patients through the end of study M96-432.

Table 3.3.7.3.2-A. Survival of M94-247 Patients Through the End of M96-432

	Ritonavir	Placebo
Patients included in analysis	543	547
Death	99	142
Censored	444	405
Hazard Ratio	0.694	
95% CI	(0.537-0.897)	
p-value	0.005[a]	
Risk Reduction[b]	30.6%	

Source IND 43718 serial 415 vol 1 page 61 and statistical table 20
[a] statistically significant at the 0.01 level
[b] 100 (1-hazard ratio)

3.3.7.4. Safety Outcomes

Eight hundred and eighteen patients were included in the safety analysis. Since patients were exposed to different lengths of treatment, safety outcomes were analyzed by treatment duration. Data from patients who discontinued drug due to adverse events were reviewed to identify possible risk factors associated with adverse events. All serious adverse events were reviewed individually. There were a total of 34 deaths during the course of this study.

3.3.7.4.1. Drug Exposure

Two hundred and eighteen, 292, 156 and 151 received 0-12 months, 12-18, 18-24 or greater than 24 months of ritonavir therapy, respectively.

3.3.7.4.2. Adverse Events

3.3.7.4.3. Overview of Adverse Events

The most common adverse events seen during the trial were diarrhea (28.9%), nausea (19.6%), asthenia (15%), upper respiratory disorder (12%), fever (11.1%), cough increase (10.4%) and rhinitis (10%).

A total of 384 (46.9%) patients prematurely discontinued from the study. Overall 89 (10.9%) of the patients discontinued due to an adverse event or HIV-related event. The most common adverse events, which lead to premature discontinuation, were diarrhea, nausea, vomiting, headache, asthenia, and circumoral paresthesia.

Table 3.3.7.4.3 summarizes the treatment-emergent adverse events occurring in > 5% of patients by the duration of ritonavir exposure regardless of attributed causality. It was difficult to discern any trends in adverse event frequencies with duration of exposure; however, it does appear that patients who have been able to continue ritonavir the longest report less circumoral parasthesia.

Table 3.3.7.4.3. Treatment-Emergent Adverse Events Occurring in > 5% of Patients

Body System	Duration of Ritonavir Exposure				
	0-12 Months (n=219)	>12-18 Months (n=292)	>18-24 Months (n=156)	> 24 Months (n=151)	Overall (n=818)
Body as a Whole					
Abdominal Pain	20 (9.1%)	26 (8.9%)	8 (5.1%)	8 (5.3%)	62 (7.6%)
Accidental Injury	9 (4.1%)	18 (6.2%)	14 (9.0%)	4 (4.6%)	48 (5.9%)
Asthenia	49 (22.4%)	39 (13.4%)	21 (13.5%)	14 (9.3%)	123 (15%)
Back Pain	5 (2.3%)	15 (5.1%)	6 (3.8%)	4 (2.6%)	30 (3.7%)
Fever	25 (11.4%)	31 (10.6%)	21 (13.5%)	14 (9.3%)	91 (11.1%)
Flu Syndrome	7 (3.2%)	25 (8.6%)	10 (6.4%)	5 (3.3%)	47 (5.7%)
Headache	28 (12.8%)	22 (7.5%)	8 (5.1%)	15 (9.9%)	73 (8.9%)
Pain	15 (6.8%)	25 (8.6%)	16 (10.3%)	9 (6%)	65 (7.9%)
Digestive System					
Anorexia	15 (6.8%)	20 (6.8%)	9 (5.8%)	2 (1.3%)	46 (5.6%)
Diarrhea	74 (33.8%)	84 (28.8%)	48 (30.8%)	30 (19.9%)	236 (28.9%)
Nausea	54 (24.7%)	52 (17.8%)	30 (19.2%)	24 (15.9%)	160 (19.6%)
Vomiting	24 (11%)	20 (6.8%)	13 (8.3%)	14 (9.3%)	71 (8.7%)
Hemic & Lymphatic System					
Lymphadenopathy	16 (7.3%)	18 (6.2%)	13 (8.3%)	8 (5.3%)	55 (6.7%)
Metabolic and Nutritional					
Weight Loss	12 (5.5%)	13 (4.5%)	11 (7.1%)	42 (2.6%)	40 (4.9%)
Nervous System					
Circumoral Paresthesia	46 (21%)	21 (7.2%)	3 (1.9%)	3 (2%)	73 (8.9%)
Depression	12 (5.5%)	22 (7.5%)	13 (18.3%)	11 (7.3%)	58 (7.1%)
Dizziness	12 (5.5%)	13 (4.5%)	7 (4.5%)	7 (4.6%)	39 (4.8%)
Insomnia	15 (6.8%)	14 (4.8%)	14 (9%)	11 (7.3%)	54 (6.6%)
Peripheral Paresthesia	25 (11.4%)	17 (5.8%)	8 (5.1%)	7 (4.6%)	57 (7%)
Respiratory System					
Bronchitis	4 (1.8%)	10 (3.4%)	9 (5.8%)	3 (2%)	26 (3.2%)
Cough Increased	15 (6.8%)	25 (8.6%)	27 (17.3%)	18 (11.9%)	85 (10.4%)
Pharyngitis	15 (6.8%)	15 (5.1%)	8 (5.1%)	7 (4.6%)	45 (5.5%)
Rhinitis	15 (6.8%)	35 (12%)	19 (12.2%)	13 (8.6%)	82 (10%)
Sinusitis	7 (3.2%)	17 (5.8%)	11 (7.1%)	6 (4%)	41 (5%)
Upper Respiratory Disorder	14 (6.4%)	34 (11.6%)	23 (14.7%)	27 (17.9%)	98 (12%)
Skin and Appendages					
Folliculitis	11 (5%)	7 (2.4%)	4 (2.6%)	0	22 (2.7%)
Pruritis	13 (5.9%)	9 (3.1%)	7 (4.5%)	4 (2.6%)	33 (4. %)
Rash	29 (13.2%)	24 (8.2%)	18 (11.5%)	5 (3.3%)	76 (9.3%)
Skin Disorder	4 (1.8%)	11 (3.8%)	8 (5.1%)	2 (1.3%)	25 (3.1%)
Sweating	12 (5.5%)	14 (4.8%)	8 (5.1%)	5 (3.3%)	39 (4.8%)
Wart	10 (4.6%)	19 (6.5%)	12 (7.7%)	7 (4.6%)	48 (5.9%)
Urogenital System					
Vaginal Hemorrhage#	1 (6.7%)	0	0	0	1 (1.6%)

Source IND 43718 serial 415 vol 1 table 9
#Percentages are based on n=15 (0-12 months), n=28 (12-18 months, n=12(>24 months and n=64 (overall) female patients

3.3.7.4.4. Serious and Life-threatening Adverse Events

Table 3.3.7.4.4.A. summarizes serious treatment-emergent adverse events other than death that were experienced by two or more patients in any 'duration of exposure' group. A total of 97 patients experienced serious adverse events during the study. There were 14% were in the 0-12 month exposure group, 11.3% in the > 12-18 month group, 11.5% in the > 18-24 month group, and 9.9% in the > 24 month exposure group. The most common serious adverse events other than death were pneumonia 2.1%, fever 1.6%, sepsis 1%, skin carcinoma 0.6% and pancreatitis 0.6%.

Table 3.3.7.4.4.A. Summary of the Most Common Serious Adverse Events Other Than Death[a]

Body System	Duration of Ritonavir Exposure				
	0-12 Months (n=219)	>12-18 Months (n=292)	>18-24 Months (n=156)	> 24 Months (n=151)	Overall (n=818)
Fever	5 (2.3%)	5 (1.7%)	2 (1.3%)	1 (0.7%)	13 (1.6%)
Sepsis	2 (0.9%)	5 (1.7%)	1 (0.6%)	0	8 (1%)
Pancreatitis	0	2 (0.7%)	2 (1.3%)	1 (0.7%)	5 (0.6%)
Pneumonia	6 (2.7%)	5 (1.7%)	3 (1.9%)	3 (2.0%)	17 (2.1%)
Skin Carcinoma	1	2 (0.7%)	2 (1.3%)	0	5 (0.6%)

Source IND 43718 serial 415 vol 1 table 11
[a] Experienced by at least five patients

Other Clinical Adverse Events
Additional information was requested for the following selected serious adverse events: myocardial infarction, vasculitis, hepatitis, LFT abnormalities, pancreatitis, diabetes, thrombotic thrombocytopenic purpura, and kidney function abnormalities. Some of these reports are summarized below.

Cardiac arrest and myocardial infarction
Two patients had myocardial infarction in this study. These cases are described below:

A 55-year-old male was hospitalized for an anterior wall myocardial infarction, confirmed ECG and CPK, after 13 months of ritonavir therapy. Ritonavir therapy was permanently discontinued due to this event. Risk factors included a family history of myocardial infarction. The patient was a non-smoker. The patient had been receiving ritonavir at a dose of 300 mg tid due to intolerance of 600 mg BID. The patient experienced both hypertriglyceridemia and hypercholesterolemia; peak triglyceride and cholesterol values of 2680 mg/dL and 418 mg/dL, respectively, occurred eight months after beginning ritonavir therapy. The patient was hospitalized

A 38-year-old male was hospitalized for myocardial infarction after 6 months of ritonavir therapy. This patient had received anabolic steroids for 2.5 years, which resulted in a 50-60 pound weight gain. The patient was a nonsmoker with a past history of alcohol use. The patient was originally randomized to receive placebo in study M94-247. While receiving placebo the patient's triglyceride levels ranged from

296 mg/dL to 515 mg/dL. After initiating ritonavir therapy, triglyceride values increased to 700 mg/dL and peaked 3 months later to 1995 mg/dL. The triglyceride levels dropped to 755 mg/dL approximately 6 months after beginning open label ritonavir. The cholesterol was reported to be 299 mg/dL. The patient presented with radiating chest pain and was diagnosed with an inferior and anterolateral ST and T wave changes consistent with myocardial infarction. It is thought that the patient may have experienced a coronary artery spasm, which lead to the myocardial infarction. Ritonavir therapy was resumed after this event and continued until the end of the study.

Comments:
To put these two cases in perspective, we reviewed postmarketing cases of cardiac arrest and MI. There have been nine reports of cardiac arrest during the postmarketing period. Five of these reports have possible alternative etiologies. Three of the remaining four cases were not on ritonavir therapy during their terminal arrest. In addition, there have been ten reports of myocardial infarction during the postmarketing period. Five of these reports provide alternative etiologies including underlying cardiac disease and anabolic steroid use. The remaining five cases include 3 reports which provide no EKG or cardiac enzyme values. One report did state "triglycerides increased". Given the nature of these reports, it is difficult to attribute these events to ritonavir therapy. However, increased triglyceride and cholesterol levels are a risk for coronary artery disease.

Based on this information it is recommended that the package insert be revised to include a statement that myocardial infarction with or without hypertriglyceridemia and/or hypercholestrolemia has been reported in patients receiving ritonavir therapy.

Pancreatitis
There were five reports of pancreatitis in this study. These are described in detail below:

A 32-year-old female was hospitalized for pancreatitis and hepatitis after 3.5 months on ritonavir. Her past medical history was significant for post transfusion hepatitis, hepatomegaly, and lymphadenopathy. This patient had no history of hypertriglyceridemia or alcohol intake. The patient presented with abdominal pain and jaundice with a total bilirubin of 16.1 µmol/L, amylase of 1772 U/L, SGOT of 264 IU/L and SGPT 264 IU/L. All medications were discontinued and the patient's symptoms subsided after 48 hours. Laboratory values were obtained approximately two weeks after the event, which revealed an SGOT of 60 IU/L, SGPT of 53 IU/L, total bilirubin of 2.8 umol/L and amylase of 397 U/L. Ritonavir was restarted approximately one month after the event and follow up laboratory values revealed an SGOT of 25 IU/L, SGPT of 26 IU/L, amylase of 56 U/L and lipase of 272 U/L. At the follow up visit one month later the SGOT was 57 IU/L, SGPT 125 IU/L, and amylase was 56 U/L.

A 33-year-old male was hospitalized for pancreatitis after 20 months of ritonavir therapy. His past medical history was significant for tuberculosis and chronic

hepatitis. The patient was a non-drinker. Concomitant medications included ddI and ZDV. The patient experienced triglyceride elevations that peaked at 15.8 mmol/L; levels were 3.52 mmol/L two weeks prior to hospitalization. All antiretroviral medications were stopped at hospitalization and the amylase value was 313 U/L and lipase was 124. The amylase level was 226 U/L at the time of discharge and ritonavir dosing was resumed. Epivir and d4T were initiated in place of ddI and ZDV at the time of discharge.

A 34-year-old male was hospitalized for pancreatitis after 7 months of ritonavir therapy, which was preceded, by approximately 6.5 months of blinded study drug in a previous study. His past medical history was significant for duodenal ulcer and helicobacter pylori, PCP, microsporidiosis, KS of the stomach and ankle, and cocaine and heroin abuse. The patient was a smoker and drank alcohol. Concomitant medications included ddI, d4T, oxazepam, loperamide, acyclovir and co-trimoxazole. The patient presented with severe upper abdominal pain and nausea and vomiting without fever. An amylase of 566 U/L was felt to be consistent with pancreatitis, possibly related to ddI or alcohol use. All antiretroviral medications were discontinued. The amylase dropped to 365 U/L; however, the abdominal pain persisted. Approximately 2 weeks later the patient became febrile with overt icterus and was diagnosed with hepatitis (SGOT of 1830 U/L, SGPT of 1105 U/L, alkaline phosphatase of 252 U/L and total bilirubin of 75 µm/L). The patient was found to have positive hepatitis B core antibody, hepatitis C antibody, and IgG for CMV and Epstein Barr Virus. The hepatitis resolved but abdominal pain persisted. The patient restarted ritonavir therapy prior to discharge and the liver function tests from an unspecified date revealed an SGOT of 123 U/L and an SGPT of 107 U/L.

A 44-year-old male was hospitalized for pancreatitis after 1 year and 6.5 months of ritonavir. The patient did not smoke or drink alcohol. The patient began ritonavir and experienced increased triglycerides over 1000 mg/dL after two weeks of therapy. The triglyceride levels peaked at 1894 mg/dL five months later. Triglyceride levels were 631 mg/dL one year later. Concomitant medications included d4T, ddI, Bactrim DS, acyclovir, testosterone, carbamazapine, Claritin, effexor, ciprofloxacin, clarithromycin, neupogen, saquinavir, Vancenase and Sudafed. The patient presented with sharp right flank pain, vomiting, anorexia, chills and fever. An abdominopelvic CT revealed an enlarged pancreatic head with peri-pancreatic fat stranding and fluid with an amylase level of 509 U/L and lipase of 180. The patient continued to spike fevers despite antibiotic therapy. The patient improved and was discharged two weeks after hospitalization. Ritonavir therapy was interrupted during this time.

A 48-year-old male was hospitalized for pancreatitis after approximately 13 months of ritonavir therapy. The patient did not drink ethanol. The patient began ritonavir therapy on 1/24/96 and experienced triglyceride elevations to 2780 mg/dL on 7/9/96, 1839 mg/dL on 10/2/96 and 2865 mg/dL on 1/7/97. Concomitant medications included ZDV, 3TC, Bactrim, mycobutin, acyclovir and clarithromycin. The patient presented with severe abdominal pain; however, the amylase and lipase values were not provided. Ritonavir therapy was discontinued on the day of hospitalization. There

was no evidence of ascites or pseudocysts. The patient was discharged two weeks later with a triglyceride level of 300 mg/dL. Ritonavir therapy was never restarted for this patient.

Comment:

Elevations in triglycerides are a recognized risk factor for pancreatitis. Three of the five cases summarized above reported increased triglyceride levels; however, the investigator assessment did not specifically state that the pancreatitis was a result of increased triglyceride levels and some of the reports included possible alternative etiologies for pancreatitis (e.g. three patients were receiving ddI concomitantly). All five patients appeared to recover upon cessation or interruption of ritonavir and other drugs. Two patients restarted ritonavir after the event.

During review of this application, the division requested that the applicant evaluate postmarketing reports describing pancreatitis. There were 32 reports of pancreatitis in the Norvir postmarketing database derived from spontaneous (n=25) and study (n=7) sources from 3/01/96-6/30/98. Abbott reports that 13 (41%) of these reports documented concomitant hypertriglyceridemia. The median triglyceride level in the setting of pancreatitis was 2155 mg/dL (range: 365-7972). Due to incomplete reporting this is likely an underestimate of the number of cases of pancreatitis and the number of cases of pancreatitis with hypertriglyceridemia.

Based on this information it is recommended that the package insert be revised to include a statement that pancreatitis with or without hypertriglyceridemia has been reported in patients receiving ritonavir therapy.

Diabetes Mellitus

A 34-year-old male was hospitalized for pneumonia and diabetes mellitus after 9.5 months of ritonavir therapy. Concomitant medications included megestrol. The patient presented with a fever, disorientation and glucose level of 860 mg/dL. Blood cultures were negative. The patient's glucose levels over the previous year were below 100 mg/dL except after episodes of an abscessed tooth, and herpes zoster when glucose levels were 155 mg/dL and 190 mg/dL, respectively. The patient started on IV antibiotics and insulin. The patient improved over time. It is not known if ritonavir therapy was continued or whether therapy for glucose control was required.

Vasculitis and Thrombotic Thrombocytopenic purpura

There was one case each of vasculitis and TTP.

Comment:
An analysis of postmarketing safety reports for TTP was conducted on January 9, 1998. There were only two reports of purpura. One report, summarized above, was described as a TTP-like event. The second report did not describe TTP; a negative

rechallenge for purpura and thrombocytopenia was noted. There are literature citations, which suggest a correlation between HIV infection and TTP. Since there is only a single report of possible TTP, revision to the package insert is not warranted at this time.

3.3.7.4.5. Adverse Events Associated with Discontinuation of Treatment

Overall 89 (10.9%) patients discontinued ritonavir due to adverse events or HIV-related events. Table 3.3.7.4.5.A. summarizes discontinuations due to adverse events. This illustrates that treatment discontinuations for adverse events tend to occur within the first 18 months of therapy.

Table 3.3.7.4.5.A. Discontinuations Due to Adverse Events

	Duration of Ritonavir Exposure				
	0-12 Months (n=219)	>12-18 Months (n=292)	>18-24 Months (n=156)	> 24 Months (n=151)	Overall (n=818)
Adverse Event or HIV-Related Event	57 (26%)	24 (8.2%)	5 (3.2%)	3 (2%)	89 (10.9%)

3.3.7.4.6. Deaths

There were a total of 34 deaths during the course of this study. Sixteen deaths occurred during treatment or up to 30 days following the last ritonavir dose and the remaining 16 patients died greater than 30 days from the last ritonavir dose. Seventeen patients died in the 0-12 month exposure group, 13 in the 12-18 group, one in the 18-24 group and 3 in the > 24 month ritonavir exposure group.

The applicant provided narratives for those deaths that occurred during treatment or up to 30 days following treatment. Of the 16 deaths that occurred during this period, nine were attributed to an AIDS-defining event. The most common AIDS-defining event that resulted in death was pneumonia (4/9 or 44.4%).

3.3.7.4.7. Laboratory Findings

Table 3.3.7.4.6. summarizes the frequency of extremely high chemistry values (at least one extreme laboratory value during the study) by duration of ritonavir exposure. The total number of patients shown for both chemistry and hematology values represents only those patients with at least one laboratory determination while on study and does not reflect the total number of patients participating in this study.

Table 3.3.7.4.6.A. Extremely High Chemistry Values by Duration of Ritonavir Exposure

Extremely High Value	Duration of Ritonavir Exposure				
	0-12 Months (n=178)	>12-18 Months (n=270)	>18-24 Months (n=153)	> 24 Months (n=151)	Overall (n=752)
Glucose (>250 mg/dL)	1 (0.6%)	5 (1.9%)	4 (2.6%)	—	10 (1.3%)
Bilirubin, total > 3.6 mg/dL)	2 (1.1%)	2 (0.7%)	—	—	4 (0.5%)
SGOT > 180 IU/L)	11 (6.2%)	11 (4.1%)	3 (2%)	1 (0.7%)	26 (3.5%)
SGPT (> 215 IU/L)	14 (7.4%)	18 (6.7%)	11 (7.2%)	3 (2%)	46 (6.1%)
Alkaline Phosphatase (>550 IU/L)	2 (1.1%)	2 (0.7%)	1 (0.%)	—	5 (0.7%)
Creatinine (> 3.6 mg/dL)	—	—	1 (0.7%)	—	1 (0.1%)
Amylase (> 2 x ULN)	3 (1.7%)	4 (1.5%)	3 (2%)	4 (2.6%)	14 (1.9%)
Uric Acid (> 12 mg/dL)	1 (0.6%)	1 (0.4%)	—	—	2 (0.3%)
Sodium (>157 mEq/L)	—	1 (0.4%)	1 (0.7%)	—	2 (0.3%)
Calcium > 12.6 mg/dL)	—	1 (0.4%)	—	—	1 (0.1%)
Triglycerides > 1500 mg/dL)	10 (5.6%)	19 (7%)	9 (5.9%)	7 (4.6%)	45 (6%)
GGT (>300 IU/L)	22 (12.4%)	49 (18.1%)	23 (15%)	13 (8.6%)	107 (14.2%)
CPK (>800 IU/L)	5 (2.8%)	16 (5.9%)	6 (3.9%)	7 (4.6%)	34 (4.5%)

Source: IND 43718 serial 415 vol 1 table 17

3.3.7.4.7.1 Laboratory Abnormalities: Mean Changes Over Time

Triglyceride

Mean triglyceride values remained elevated above the upper limit of normal throughout the study. The applicant stated that there was no suggestion of greater increases in triglycerides with longer ritonavir exposure. Forty-five patients (6%) had reported triglyceride levels > 1500 mg/dL.

Glucose

Mean glucose levels generally remained stable.

3.3.8. CONCLUSIONS

3.3.8.1.Efficacy

Plasma HIV RNA was not routinely assayed for the majority of the patients in this study. CD4 cell counts were used as an assessment of efficacy. All four groups showed stable to increasing CD4 cell counts throughout the study. CD4 cell count increases did not appear to be limited to patients who started with higher CD4 cell counts.

Thirty-four deaths occurred during this study. The applicant reports that the relative survival benefit for patients who initially received ritonavir compared to placebo in study M94-247 was apparent even at the end of study M96-432.

3.3.8.2. Safety

The overall safety profile of ritonavir therapy observed in this study is similar to other phase 2 and 3 trials. Patients in group 1 (< 12 months) had the highest rate of gastrointestinal symptoms, asthenia and paresthesias. Group 1 also had the highest rate of discontinuation due to adverse events or HIV-related events. Overall the most common adverse events were diarrhea, nausea, asthenia, upper respiratory disorder, fever, increased cough and rhinitis. The frequencies of abdominal pain, asthenia, anorexia, diarrhea, nausea, paresthesias, folliculitis and rash were lower among patients with longer-term exposure. This probably reflects a selection bias, in which patients who tolerated drug stayed on drug longer, rather than an actual reduction in adverse events with prolonged use.

Laboratory abnormalities were similar in this study as compared to previous ritonavir studies. Increased liver function tests and triglyceride levels (6% > 1500 mg/dL) were observed; however, these levels did not appear to be related to duration of ritonavir therapy. There were 3 cases of pancreatitis in-patients with elevated triglycerides. In addition there were two patients who suffered M.I. A causal effect of ritonavir cannot be excluded.

3.4 Study M96-462

3.4.1. Study Title

"Safety and Efficacy of Ritonavir in Combination with Saquinavir in HIV-Infected Patients."

3.4.2. Objectives:

The primary objectives of this study were to assess the safety and efficacy of various combination regimens of ritonavir and saquinavir. Secondary objectives included assessment of pharmacokinetic profiles.

3.4.3. Study Design

Study M96-462 was a multi-dose, open-label, randomized, multicenter trial in 141 HIV-infected patients with CD4 cell counts of 100-500 cells/mm^3. Patients were randomized as follows:

Group 1
Arm A: ritonavir 400 mg BID + saquinavir 400 mg BID
Arm B: ritonavir 600 mg BID + saquinavir 400 mg BID

Group 2
Arm C: ritonavir 400 mg TID + saquinavir 400 mg TID
Arm D ritonavir 600 mg BID + saquinavir 600 mg BID

The protocol required an antiviral washout period of two weeks prior to initiation of study medications.

Patients who experienced virologic failure after the week-12 study visit were given the option of adding one or two nucleoside reverse transcriptase inhibitors (NRTIs) to their regimen. Virologic failure was defined as HIV RNA > 200 copies/mL at 12 weeks or HIV RNA < 200 copies/mL followed by rebound defined as two consecutive HIV RNA values > 200 copies/mL.

Patients were assessed for adverse events, laboratory tests (chemistry and hematology); plasma HIV RNA and CD4 cell counts at weeks 2, 4, 6, 8, 12, 16, 20, 24, 30, 36, 42, and 48 weeks.

Patients were given the option of participating in a 52-week extension phase in which they would receive ritonavir 400 mg BID + saquinavir 400 mg BID.

3.4.4. Patient Population

3.4.4.1. Inclusion Criteria

The eligibility criteria included male and female HIV-infected patients aged 12 and older. Patients were required to be protease-inhibitor naïve with CD4 cell counts of 100 - 500 cells.

3.4.4.2. Exclusion Criteria

Patients with a history of significant drug hypersensitivity, active substance abuse, acute or chronic pancreatitis or with abnormal laboratory findings at screening (hemoglobin < 8.5 g/dL, absolute neutrophil count < 1000 cells/µL, platelet count < 50,000 per u/L, ALT/AST > 2.5X ULN, creatinine > 1.5X ULN, pancreatic amylase >

ULN, fasting triglyceride > 400 mg/dL) were to be excluded. Pregnancy, breast-feeding, and inadequate contraception were also reasons for exclusion.

3.4.5. Study Endpoints

3.4.5.1. Primary Endpoints

The primary endpoint was the duration of virologic response. The applicant defined the duration of response as the time from the onset of response (i.e., the first two consecutive HIV RNA measurements documenting a decrease of at least one $\log_{10}$ from baseline or below 200 copies/mL) to the time of virologic failure.

The primary immunologic endpoint was the change in absolute CD4 and CD8 cell counts.

3.4.5.2.Secondary Endpoints

Additional endpoints included change from baseline in Karnofsky performance, and quality of life.

3.4.6. Analytical and Statistical Plans

3.4.6.1. Efficacy

The proportion of patients with viral load below the limit of assay quantification was analyzed using the Fisher's exact test for each study visit. These data were analyzed using "on-study" and "intent-to-treat" approaches.

3.4.6.2. Safety

The proportion of patients with treatment-emergent adverse events was summarized within each treatment arm by severity and causality. Adverse events resulting in premature discontinuations from study drug were also summarized within each treatment arm.

For laboratory parameters (hematology, clinical chemistry and baseline urinalysis), shifts from baseline (ACTG grading system) were tabulated by treatment group.

3.4.7. Results

3.4.7.1. Patient Disposition

A total of 141 patients were enrolled into this trial. Table 3.4.7.1.A summarizes the applicant's assessment of the number of patients evaluable for safety and efficacy during the 48-week treatment period.

Table 3.4.7.1.A Patient Disposition

	Group I		Group II	
TREATMENT ARM	**A**	**B**	**C**	**D**
Ritonavir + Saquinavir	**400 mg BID 400 mg BID**	**600 mg BID 400 mg BID**	**400 mg TID 400 mg TID**	**600 mg BID 600 mg BID**
All Randomized Patients	35	36	33	37
Prematurely Discontinued[a]	5	8 (2)	11	11 (5)
Continuing on Study	30	28	22	26
Continuing on Randomized Dosage	28	17	12	13
Continuing on Reduced Dosages[a]	0	10 (8)	10 (9)	12 (7)
Continuing on Dose Interruption	1	0	1	0
Other	1[b]	1[c]	0	0
Added Other Antiretrovirals at Any Time During the Study	8	4	5	11

Source: IND 43,718 serial 409 vol 1 page 45

[a] Numbers in parentheses indicate the number of patients who switched to RTV 400 mg BID and SQV 400 mg BID

[b] Increased ritonavir dose in violation of protocol

[c] For tolerability reasons ritonavir dose decreased from 600 mg to 200 mg BID and saquinavir dose increase from 400 mg to 600 mg BID

3.4.7.1.1. Reasons for Premature Discontinuation

One hundred and six patients (75%) received study therapy through week 48. Table 3.4.7.1.1.A. shows the applicant's analysis of premature discontinuations. The applicant reports that the lowest frequency of study drug discontinuation due to an adverse event was reported for patients in arm A (1/35 or 3%).

Table 3.4.7.1.1.A. Primary Reasons for Premature Discontinuation

	GROUP 1		GROUP 2	
	Arm A	Arm B	Arm C	Arm D
	RIT 400 mg BID SAQ 400 mg BID	RIT 600 mg BID SAQ 400 mg BID	RIT 400 mg TID SAQ 400 mg TID	RIT 600 mg BID SAQ 600 mg BID
Total Patients Discontinued	5	8	11	11
Reasons for Discontinuation				
Personal Reasons	3	0	1	1
Lost to Follow Up	0	1	1	3
Adverse Event	1	6[a]	9	6
Other	1	1	0	1

Source IND 43718 serial 409 vol 1 page 53 table 5, vol 3-4 appendix B Table 33

[a]One patient experienced both an adverse event and an HIV-related event leading to discontinuation

3.4.7.2. Demographic Data

Table 3.4.7.2.A. shows demographic data, baseline HIV RNA levels and CD4 cell counts.

Table 3.4.7.2.A. Demographics

	GROUP I	GROUP I	GROUP 2	GROUP 2
	Arm A	Arm B	Arm C	Arm D
	RIT 400 mg BID SAQ 400 mg BID	RIT 600 mg BID SAQ 400 mg BID	RIT 400 mg TID SAQ 400 mg TID	RIT 600 mg BID SAQ 600 mg BID
Mean age, Yrs	39	39	38	39
Men, %	77	92	91	84
Race or Ethnicity, #				
White	33	29	25	29
Black	1	3	3	5
Hispanic	1	3	4	3
Asian	0	1	1	0
Prior antiretrovirals (median)	2	2	2	2
Baseline median plasma HIV RNA, log_{10} copies/mL	4.6	4.7	4.5	4.6
Baseline median CD4 (cells/mm^3)	277	264	300	266

Source IND 43718 serial 409 vol 1 page 50

3.4.7.3. Efficacy Outcomes

The design of this study does not fulfil the division's criteria for the type of studies that warrant inclusion in the Description of Clinical Studies section of the package insert. Specifically, the study lacked a control arm, had inadequate statistical power, and included protocol procedures that confounded interpretation of results (see below). Despite these limitations, the study did demonstrate durable virologic suppression of ritonavir in combination with saquinavir in "less advanced" HIV infected individuals.

The following summarizes the applicant's on-study and intent-to-treat analyses for the proportion of patients with plasma HIV RNA below the limit of assay quantification and for mean changes in plasma HIV RNA and CD4 cell counts at week 48.

It is important to note that the results are confounded by the following variables:

1. Several patients in arm C, had their regimen altered to ritonavir 400 mg BID in combination with saquinavir 800 mg BID at different time points.

2. Several patients in arm D, reduced their doses to ritonavir 400 mg BID + saquinavir 400 mg BID at different time points.

3. Patients were allowed to add up to two reverse transcriptase inhibitors to their regimen after week 12 if patients met the criteria for virologic failure. Twenty-eight patients (19.8%) added reverse transcriptase inhibitors to their regimen. Thirty-nine percent of the patients who added reverse transcriptase inhibitors were randomized to arm D. The median time for adding an NRTI was 26 weeks after the start of treatment (median for arm D was 20 weeks and for arm A was 34 weeks).

4. Sixty-five patients either had a dosage change and/or dose interruption during the study.

Table 3.4.7.3.A. summarizes FDA's analysis of those patients who had a dosage change and/or dose interruption during the study and the reasons for these changes by treatment group. In addition, Table 3.4.7.3.A. also summarizes patient disposition with regard to dosing changes/interruptions. Overall a total of 77 patients (55%) had a dosage change and/or dose interruption during the 48-week study period. Fifty-six patients (73%) changed their dose or had a dose interruption due to adverse events; the remaining had dose changes attributed to "other reasons." The majority of the "other reasons" were listed as adherence issues for the three times a day dosing regimen.

Table 3.4.7.3.A. Number of Patients with Dose Change/Interruption and Outcome

	GROUP I		GROUP 2	
	Arm A	Arm B	Arm C	Arm D
	RIT 400 BID/ SAQ 400 mg BID (n=35)	RIT 600 mg BID/ SAQ 400 mg BID (n=36)	RIT 400 mg TID/ SAQ 400 mg TID (n=33)	RIT 600 mg BID/ SAQ 600 mg BID (n=37)
Dose change/interruption due to Adverse Event due to Other Reasons	12 9 3	17 14 3	22 11 10	25 22 3
# pts with dose change/interruption and prematurely discontinued therapy	4	5	4	8
# pts with NO dose change/interruption and prematurely discontinued therapy	1	3	6	3
Total # pts who completed 48 weeks of therapy	30	28	22	26
# pts with NO dose change/interruption and completed 48 weeks of therapy	22	16	10	9
# pts with dose change/interruption and completed 48 weeks of therapy	7	12	12	17

Source IND 43718 serial 409 vol 1 Figures 1-4 and vol 6 Appendix C.14.B.

Table 3.4.7.3.B. summarizes the applicant's on study and intent-to-treat analyses for the proportion of patients with plasma HIV RNA levels below 200 copies/mL at week 48.

Table 3.4.7.3.B. Proportion of Patients with HIV RNA < 200 copies/mL At Week 48

	GROUP I		GROUP 2	
	Arm A	Arm B	Arm C	Arm D
Regimen	RIT 400 BID/ SAQ 400 mg BID	RIT 600 mg BID/ SAQ 400 mg BID	RIT 400 mg TID/ SAQ 400 mg TID	RIT 600 mg BID/ SAQ 600 mg BID
On-Study Analysis				
Sample Size	28	26	22	27
Proportion	89%	88%	82%	96%
95% CI	(71%, 97%)	(69%, 97%)	(59%, 94%)	(79%, 100%)
Intent-To-Treat Analysis				
Sample Size	35	34	33	37
Proportion	74%	68%	55%	70%
95% CI	(56%, 87%)	(49%, 82%)	(37%, 71%)	(53%, 84%)

Source: IND 43,718 serial 409 Table 7.A vol 1 page 61

The sponsor conducted a supplemental analysis in which patients who added NRTIs were considered treatment failures. Table 3.4.7.3.C. summarizes the results from this analysis. Twenty-eight patients added reverse transcriptase inhibitors to their original study regimen. It should be noted that in Arm A, four patients chose to add reverse transcriptase inhibitors despite HIV RNA levels < 400 copies/mL (range 0-400 copies/mL).

Table 3.4.7.3.C. Proportion of Patients with HIV RNA Levels ≤ 200 copies/mL at Week 48 and Without Treatment Intensification

	GROUP I		GROUP 2	
	Arm A	Arm B	Arm C	Arm D
Regimen	RIT 400 BID/ SAQ 400 mg BID	RIT 600 mg BID/ SAQ 400 mg BID	RIT 400 mg TID/ SAQ 400 mg TID	RIT 600 mg BID/ SAQ 600 mg BID
Week 48	20/28 (71.4%)	19/26 (73.1%)	14/22 (63.6%)	17/27 (63%)

Source IND 43,718 serial 409 Stat table 13.B, Appendix C.14.D, C.15 and C.16

Table 3.4.7.3.D. summarizes the average change from baseline for plasma HIV RNA at weeks 12, 24 and 48.

The applicant reports that the median increase in CD4 cells was approximately 128 cells/mm^3 at week 48. Overall there was an increase in CD4 cell counts seen in all treatment groups through week 48.

3.4.7.4.1 Safety Outcomes

All 141 patients were included in the safety analysis. Data from patients who discontinued drugs due to adverse events were reviewed to identify possible risk factors associated with adverse events. All serious adverse events were reviewed individually. There were no deaths in this study.

3.4.7.4.1.1. Drug Exposure

The extent of drug exposure up to week 48 is described in Table 3.4.7.4.1.1.A. It is important to note that this table does not reflect time on the original randomized treatments since several patients in arms C and D had their regimens altered. The median duration of exposure to ritonavir and saquinavir was 364 days. The majority of patients received greater than 336 days of drug exposure. There was no difference between the duration of drug exposure for ritonavir or saquinavir.

Table 3.4.7.4.1.1.A. Summary of Drug Exposure to Ritonavir and Saquinavir

	GROUP I		GROUP 2	
	Arm A	Arm B	Arm C	Arm D
Study Drug Exposure	RIT 400 BID/ SAQ 400 mg BID (n=35)	RIT 600 mg BID/ SAQ 400 mg BID (n=36)	RIT 400 mg TID/ SAQ 400 mg TID (n=33)	RIT 600 mg BID/ SAQ 600 mg BID (n=37)
1-14 days	1 (2.9%)	1 (2.8%)	4 (12.1%)	0 (0%)
> 14-56 days	0 (0%)	1 (2.8%)	6 (18.2%)	1 (2.7%)
> 56-112 days	2 (5.7%)	2 (5.6%)	1 (3.0%)	5 (13.5%)
> 122-168 days	1 (2.9%)	3 (8.3%)	0 (0%)	2 (5.4%)
> 168-224 days	1 (2.9%)	1 (2.8%)	0 (0%)	2 (5.4%)
> 224-280 days	1 (2.9%)	0 (0%)	0 (0%)	3 (8.1%)
> 280-336 days	0 (0%)[a]	0 (0%)	0 (0%)	1 (2.7%)
> 336 days	29[b]	28 (77.8%)	22 (66.7%)	23 (62.2%)
Median Duration (days)	364	364	364	364
Range (days)	7 to 364	9 to 364	1 to 364	30 to 364

Source: IND 43,718 serial 409 Table 8 vol 1 page 73

[a] 1 (2.9%) for saquinavir
[b] 28 (80%) for saquinavir

3.4.7.4.1.2. Adverse Events

3.4.7.4.1.3. Overview of Adverse Events

All 141 patients experienced at least one adverse event. The most common adverse events seen during the trial were diarrhea (92%), asthenia (62%), nausea (62%), circumoral paresthesia (83%), lymphadenopathy (50%), and peripheral paresthesia (45%).

Twenty-two (16%) of the patients enrolled discontinued study regimens due to adverse events. The most common adverse events that led to premature discontinuation were diarrhea and nausea. The applicant noted that vasodilatation; hyperesthesia and paresthesia occurred less frequently in arm A than arm B. Arm A also had the lowest number of discontinuations due to adverse event, 1/35 (3%).

Grade 3 or 4 increases in SGPT were seen in 9.2% (13/141) of all patients randomized. Of these grade 3 or 4 increases in SGPT, 22% (8/37) of patients randomized to arm D experienced increases in liver function tests. Eight (6%) of patients developed triglyceride levels > 1500 mg/dL.

Table 3.4.7.1.3.A. summarizes treatment-emergent events (any intensity) without regard to causality and occurring in greater than 5 patients during the 48-week treatment period. Table 3.4.7.1.3.B. summarizes treatment-emergent events (any intensity) that are of probable, possible or unknown relationship to study drug and that occurred in greater than 5 patients during the 48 week treatment period. Adverse events are presented according to original randomized treatment arm regardless of modifications to the regimen.

Table 3.4.7.1.3.A. Treatment Emergent Events Without Regard To Causality

	GROUP I		GROUP 2	
	Arm A	Arm B	Arm C	Arm D
	RIT 400 BID/ SAQ 400 mg BID (n=35)	RIT 600 mg BID/ SAQ 400 mg BID (n=36)	RIT 400 mg TID/ SAQ 400 mg TID (n=33)	RIT 600 mg BID/ SAQ 600 mg BID (n=37)
All Body Systems				
Total Patients with any sign/symptom	35 (100%)	36 (100%)	32 (97.0%)	37 (100%)
Body As A Whole				
Abdominal pain	7 (20%)	9 (25%)	12 (36.4%)	10 (27%)
Accidental injury	4 (11.4%)	6 (16.7%)	5 (15.2%)	1 (2.7%)
Asthenia	23 (65.7%)	21 (58.3%)	21 (63.6%)	23 (62.2%)
Fever	3 (8.6%)	3 (8.3%)	8 (24.2%)	13 (35.1%)
Flu syndrome	11 (34.4%)	3 (8.1%)	3 (9.1%)	10 (27%)
Headache	11 (31.4%)	10 (27.8%)	12 (36.4%)	12 (32.4%)
Pain	9 (25.7%)	5 (13.9%)	9 (27.3%)	10 (27%)
Cardiovascular System				
Vasodilatation	7 (20%)	19 (52.8%)	7 (21.2%)	19 (51.4%)
Digestive System				
Anorexia	9 (25.7%)	8 (22.2%)	6 (18.2%)	16 (43.2%)
Diarrhea	31 (88.6%)	33 (91.7%)	30 (90.9%)	36 (97.3%)
Dry Mouth	0 (0%)	2 (5.6%)	5 (15.2%)	7 (18.9%)
Dyspepsia	5 (14.3%)	8 (22.2%)	5 (15.2%)	6 (16.2%)
Flatulence	5 (14.3%)	7 (19.4%)	12 (36.4%)	20 (54.2%)
Liver Function Test Abnormal	2 (5.7%)	1 (2.8%)	0 (0%)	6 (16.2%)
Mouth Ulcer	8 (22.9%)	4 (11.1%)	4 (12.1%)	3 (8.1%)
Nausea	19 (54.3%)	22 (61.1%)	21 (63.6%)	25 (67.6%)
Vomiting	9 (25.7%)	8 (22.2%)	11 (33.3%)	13 (35.1%)
Hemic And Lymphatic System				
Lymphadenopathy	20 (57.1%)	20 (55.6%)	11 (33.3%)	19 (51.4%)
Musculoskeletal System				
Arthralgia	5 (14.3%)	2 (5.6%)	3 (9.1%)	4 (10.8%)
Myalgia	4 (11.4%)	3 (8.3%)	1 (3%)	6 (16.2%)
Nervous System				
Amnesia	0 (0%)	2 (5.6%)	4 (12.1%)	5 (13.5%)
Anxiety	7 (20%)	1 (2.8%)	5 (15.2%)	1 (2.7%)
Circumoral paresthesia	28 (80%)	31 (86.1%)	25 (75.8%)	33 (89.2%)
Depersonalization	5 (14.3%)	6 (16.7%)	2 (6.1%)	1 (2.7%)
Depression	6 (17.1%)	5 (13.9%)	8 (24.2%)	10 (27%)
Dizziness	9 (25.7%)	14 (38.9%)	12 (36.4%)	12 (32.4%)
Hyperesthesia	2 (5.7%)	9 (25%)	7 (21.2%)	8 (21.6%)
Insomnia	5 (14.3%)	6 (16.7%)	4 (12.1%)	9 (24.3%)
Paresthesia	2 (5.7%)	9 (25%)	5 (15.2%)	8 (21.6%)
Peripheral paresthesia	16 (45.7%)	18 (50%)	13 (39.4%)	16 (43.2%)
Somnolence	1 (2.9%)	6 (16.7%)	0 (0%)	3 (8.1%)
Thinking Abnormal	4 (11.4%)	5 (13.9%)	3 (9.1%)	8 (21.6%)
Respiratory System				
Cough Increased	8 (22.9%)	4 (11.1%)	4 (12.1%)	11 (29.7%)
Dyspnea	1 (2.9%)	2 (5.6%)	3 (9.1%)	5 (13.5%)
Lung Disorder	1 (2.9%)	7 (19.4%)	3 (9.1%)	3 (8.1%)
Pharyngitis	6(17.1%)	11 (30.6%)	11 (33.3%)	18 (48.6%)
Rhinitis	7 (20%)	6 (16.7%)	5 (15.2%)	13 (35.1%)
Sinusitis	(0%)	2 (5.6%)	4 (12.1%)	6 (16.2%)
Skin and Appendages				
Acne	2 (5.7%)	6 (16.7%)	3 (9.1%)	5 (13.5%)
Rash (Maculopapular Rash,	11(31.4%)	11 (29.7%)	12 (36.7%)	25 (67.6%)

Folliculitis, Vesiculobullous Rash)				
Special Senses				
Taste Perversion	14 (40%)	11 (30.6%)	13 (39.4%)	17 (45.9%)
Urogenital System				
Nocturia	4 (11.4%)	1 (2.8%)	4 (12.1%)	7 (18.9%)

Source IND 43718 serial 409 vol 3 Statistical Table 29

Table 3.4.7.1.3.B. Treatment Emergent Events: Probable, Possible or Unknown Relationship

	GROUP I		GROUP 2	
	Arm A	Arm B	Arm C	Arm D
	RIT 400 BID/ SAQ 400 mg BID (n=35)	RIT 600 mg BID/ SAQ 400 mg BID (n=36)	RIT 400 mg TID/ SAQ 400 mg TID (n=33)	RIT 600 mg BID/ SAQ 600 mg BID (n=37)
All Body Systems				
Total Patients with any sign/symptom	35 (100%)	36 (100%)	32 (97.0%)	140 (99.3%)
Body As A Whole				
Abdominal pain	6 (17.1%)	7 (19.4%)	10 (30.3%)	6 (16.2%)
Asthenia	19 (54.3%)	21 (58.3%)	21 (63.6%)	23 (62.1%)
Fever	0 (0%)	1 (2.8%)	0 (0%)	6 (16.2%)
Headache	7 (20%)	8 (22.2%)	11 (33.3%)	10 (27%)
Pain	3 (8.6%)	2 (5.6%)	5 (15.2%)	
Cardiovascular System				
Vasodilatation	7 (20%)	19 (52.8%)	7 (21.2%)	18 (48.6%)
Digestive System				
Anorexia	7 (20%)	8 (22.2%)	5 (15.2%)	14 (37.8%)
Diarrhea	30 (85.7%)	33 (91.7%)	30 (91%)	36 (97.3%)
Dry Mouth	0 (0%)	2 (5.6%)	4 (21.1%)	6 (16.2%)
Dyspepsia	5 (14.3%)	6 (16.7%)	3 (9%)	6 (16.2%)
Flatulence	5 (14.3%)	7 (19.4%)	12 (36.3%)	20 (54.1%)
Liver Function Test Abnormal	1 (2.9%)	1 (2.8%)	0 (0%)	5 (13.5%)
Nausea	18 (51.4%)	22 (61.1%)	30 (91%)	22 (59.5%)
Vomiting	8 (22.9%)	5 (13.9%)	8 (24.2%)	6 (16.2%)
Musculoskeletal System				
Myalgia	3 (8.6%)	1 (5.6%)	0 (0%)	5 (13.5%)
Nervous System				
Amnesia	0 (0%)	2 (5.6%)	2 (6.1%)	5 (13.5%)
Circumoral paresthesia	28 (80%)	31 (86.1%)	25 (75.8%)	33 (89.2%)
Depersonalization	5 (14.3%)	6 (16.7%)	2 (6.1%)	1 (2.7%)
Depression	1 (2.9%)	4 (11.1%)	6 (18.2%)	8 (21.6%)
Dizziness	8 (22.9%)	13 (36.1%)	12 (36.3%)	12 (32.4%)
Hyperesthesia	2 (5.7%)	9 (25%)	7 (21.2%)	7 (19%)
Insomnia	3 (8.6%)	5 (13.9%)	3 (9.1%)	6 (16.2%)
Paresthesia	2 (5.7%)	8 (22.2%)	5 (15.2%)	8 (21.6%)
Peripheral Paresthesia	14 (40%)	16 (44.4%)	13 (39.4%)	15 (41%)
Thinking Abnormal	2 (5.7%)	5 (13.9%)	3 (9.1%)	8 (21.6%)
Respiratory System				
Pharyngitis	3 (8.6%)	7 (19.4%)	8 (24.2%)	9 (24.3%)
Rhinitis	1 (2.9%)	1 (2.8%)	5 (15.2%)	5 (13.5%)
Skin and Appendages				
Acne	1 (2.9%)	3 (8.3%)	2 (6.1%)	5 (13.5%)
Rash (Maculopapular Rash, Folliculitis, Vesiculobullous Rash)	7 (19.4%)	9 (25%)	7 (21.2%)	10 (37%)

Special Senses				
Taste Perversion	14 (40%)	11 (30.6%)	13 (39.4%)	17 (46%)
Urogenital System				
Nocturia	3 (8.6%)	1 (2.8%)	4 (21.1%)	7 (19%)

source IND 43718 serial 409 vol 3 Statistical Table 30

3.4.7.4.1.4. Serious and Life-threatening Adverse Events

Table 3.4.7.4.1.4.A. lists all patients with serious adverse events throughout the 48-week study period. A total of 29 serious adverse events were reported in 16 patients through week 48 of this study. Four of the serious adverse events resulted in premature discontinuations from the study. Of the 29 serious adverse events, 17 were considered unrelated, 1 probably not related, 6 possibly related, and 5 probably related by investigators. Events that were considered to be at least possibly related are shown in the table below.

Table 3.4.7.4.1.4.A. Serious Adverse Events (at least possibly related)

PATIENT	TREATMENT	ONSET (DAYS)	REASON	SEVERITY	CAUSALITY	ACTION TAKEN
1015	400/400 BID	48	Vasospasm	Severe	Probable	Hospitalization
2019	600/600 BID	85 101	SGPT Increase SGOT Increase Hyperbilirubinemia Hepatitis* Abdominal Pain	Severe Severe Moderate Severe Mild	Possible	Hospitalization
2043	600/600 BID	17	Accidental Overdose Dizziness Larynx Edema Paresthesia Sweating	Moderate Moderate Moderate Moderate Moderate	Not related Probable Probable Probable Probable	None
2061	600/600 BID	18	Ileus	Severe	Possible	Hospitalization
2067	600/600 BID	70	Accidental Overdose Local Throat Irritation	Moderate Moderate	Not related Possible	None

*Patient prematurely discontinued for this serious adverse event
Source: IND 43,718 serial 409 vol 1 Table 10 and vol 7-8 Appendix C.18.A. and Appendix C.18.B.

There was one serious drug interaction between ritonavir/saquinavir and ergotamine that resulted in peripheral vasoconstriction and cyanosis. Three days after the patient received ergotamine for a migraine headache the patient presented with cyanotic extremities to an outpatient clinic. Five days after the symptoms appeared the patient was hospitalized and received nitroprusside treatment for persistent vasoconstriction. The symptoms resolved without sequelae. Ritonavir and saquinavir were interrupted during this event and subsequently restarted. The patient remained on study therapy through the 48-week study period.

Shortly after this event was reported to FDA, ergot derivatives were added to the contraindicated medication list in the Norvir package insert.

3.4.7.4.1.5. Adverse Events Associated with Premature Discontinuation of Treatment

3.4.7.4.1.6. Serious Adverse Events

The applicant reported three patients who prematurely discontinued randomized treatment due to a serious adverse event, of which only one event was possibly related to the use of ritonavir/saquinavir. The patient was discontinued from the study on day 141 due to signs and symptoms of hepatitis (SGOT =814 U/L, SGPT =812 U/L, bilirubin =10.1 mg/dL). No rechallenge was attempted

3.4.7.4.1.7. Non-Serious Adverse Events

The applicant stated that a total of 22 patients withdrew from the study due to adverse events. Three patients discontinued treatment for adverse events between weeks 24 and 48. However FDA's analysis noted that 31 patients withdrew from the study due

to adverse events, 28 patients for non-serious adverse events and 3 patients for serious adverse events (described in section 3.4.7.4.1.4). At the time of discontinuation from study drug, the majority of these patients had an ongoing or unresolved adverse event such as diarrhea, nausea, fatigue or circumoral paresthesia. Table 3.4.7.4.1.7.A and B displays reasons for premature discontinuations as analyzed by the applicant and FDA, respectively. In FDA's analysis patients who had an ongoing or unresolved adverse event at the time of drug discontinuation were classified as prematurely discontinuing therapy due to an adverse event.

Table 3.4.7.4.1.7.A. Applicant's Analysis of Primary Reasons for Premature Discontinuation

Reasons for Discontinuation	GROUP I		GROUP II	
	Arm A	Arm B	Arm C	Arm D
	RIT 400 BID/ SAQ 400 mg BID	RIT 600 mg BID/ SAQ 400 mg BID	RIT 400 mg TID/ SAQ 400 mg TID	RIT 600 mg BID/ SAQ 600 mg BID
Total Patients Discontinued	5	8	11	11
Personal Reasons	3	0	1	1
Lost to Follow Up	0	1	1	3
Adverse Event	1	6[a]	9	6
Other	1	1	0	1

Source IND 43718 serial 409 vol 1 page 53 table 5, vol 3-4 appendix B Table 33
[a]One patient experienced both an adverse event and an HIV-related event leading to discontinuation

Table 3.4.7.4.1.7.A. FDA's Analysis of Primary Reasons for Premature Discontinuation

Reasons for Discontinuation	GROUP I		GROUP II	
	Arm A	Arm B	Arm C	Arm D
	RIT 400 BID/ SAQ 400 mg BID	RIT 600 mg BID/ SAQ 400 mg BID	RIT 400 mg TID/ SAQ 400 mg TID	RIT 600 mg BID/ SAQ 600 mg BID
Total Patients Discontinued	5	8	11	11
Adverse Event	2	9[a]	10	10
Personal Reasons; Lost to Follow Up or Other	3	0	1	1

Source IND 43718 serial 409 vol 1 page 53 table 5, vol 3-4 appendix B Table 33
[a]One patient experienced both an adverse event and an HIV-related event leading to discontinuation

3.4.7.4.1.8. Deaths

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

3.4.7.4.1.7. Laboratory Findings

3.4.7.4.1.7.1. Biochemistry

Glucose

There were no clinically significant changes in glucose. However patient 1033, randomized to arm A had a baseline glucose value of 256 mg/dL that continued to

increase to a peak glucose level of 407 mg/dL on day 343. It is unclear if this general increase was related to the treatment regimen.

Liver Function Tests

Table 3.4.7.4.1.7.1.A. displays the number of patients with Grade 3 or 4 elevations in SGPT/SGOT. Fourteen patients experienced grade 3 or 4 increases in SGPT/SGOT. The majority of these cases (8 of 14) occurred in patients who were randomized to Arm D. The remaining 6 cases were equally distributed among arms A-C.

Of the 14 patients who experienced grade 3 or 4 SGPT/SGOT elevations, 4 patients were HCV Ab+ at baseline and 5 patients were HBSAg+ at baseline. The majority (78%) had transaminase elevations during the first three months of treatment. The applicant calculated that the relative risk for developing grade 3 or 4 elevation in SGPT/SGOT was associated with baseline abnormalities in serum hepatic transaminases or baseline seropositivity for HBSAg or HCV Ab (relative risk = 5.0; 95% CI: 1.5, 16.9).

Table 3.4.7.4.1.7.1.A. Grade 3 or 4 Elevations in SGPT/SGOT

	GROUP I		GROUP II	
	Arm A	Arm B	Arm C	Arm D
Lab Event (Grade 3 or 4)	RIT 400 BID/ SAQ 400 mg BID (n=35)	RIT 600 mg BID/ SAQ 400 mg BID (n=36)	RIT 400 mg TID/ SAQ 400 mg TID (n=33)	RIT 600 mg BID/ SAQ 600 mg BID (n=37)
↑ SGOT and/or SGPT	2# (6%)	2 (6%)	2 (6%)	8 (21%)
↑ SGOT	2#	1	2	6
↑ SGPT	2#	2	1	8

Source: IND 43,718 serial 409 vol 1, Table 11

Includes one patient who dose escalated ritonavir to 600 mg bid and one patient with acute hepatitis A

Triglycerides

The applicant reports that statistically significant increases over baseline in triglyceride levels persisting throughout the 48-week treatment period were observed for all treatment arms. The mean peak increase was observed at week 8, then diminished but remained elevated throughout the study. Sixteen patients developed grade 3 or 4 (> 1500 mg/dL) elevations in triglyceride levels. Six patients had experienced an increase in triglycerides of greater than 2000 mg/dL and one patient had an increase in triglycerides of greater than 3000 mg/dL. There was no case of hypertriglyceridemia-associated pancreatitis and no patients discontinued study treatment for elevated triglycerides. Table 3.4.7.4.1.7.1.B. summarizes peak triglyceride levels by treatment group. Twenty-six patients (18.4%) experienced peak triglyceride levels of greater than 1000 mg/dL during the study.

Table 3.4.7.4.1.7.1.B. Elevations in Triglyceride Levels

	GROUP I		GROUP II		TOTAL
	Arm A	Arm B	Arm C	Arm D	Arms A-D
	RIT 400 mg BID + SAQ 400 mg BID (n=35)	RIT 600 mg BID + SAQ 400 mg BID (n=36)	RIT 400 mg TID + SAQ 400 mg TID (n=33)	RIT 600 mg BID +SAQ 600 mg BID (n=37)	(n=141)
Triglyceride value > 800 mg/dL	6 (17.1%)	9 (25%)	9 (27.3%)	9 (24.3%)	33 (23.4%)
Triglyceride value > 1500 mg/dL	4 (11.4%)	4 (11.1%)	3 (9.1%)	5 (13.5%)	16 (11.3%)
Triglyceride value 1000-1499 mg/dL	2 (5.7%)	2 (5.6%)	4 (12.1%)	3 (8.1%)	10 (7.1%)
Triglyceride value 1500-2000 mg/dL	2 (5.7%)	2 (5.6%)	3 (9.1%)	3 (8.1%)	10 (7.1%)
Triglyceride value > 2001 mg/dL	2 (5.7%)	2 (5.6%)	0	2 (5.4%)	6 (4.3%)

Source: IND 43718 serial 409 vol 12 appendix C.21.D and vol 13 appendix C.21.E. and IND serial 466

Six patients received antihyperlipidemic agents as a result of elevated triglycerides. Table 3.4.7.4.1.7.1.C. displays the effect of antihyperlipidemic agents on triglyceride levels.

Table 3.4.7.4.1.7.1.C. Effect of Antihyperlipidemic Agents on Triglyceride Levels

PATIENT ID	TREATMENT ARM	ANTIHYPERLIPIDEMIC DRUG INTERVENTION	PRE-INTERVENTION MAXIMUM LEVEL (MG/DL)	POST-INTERVENTION LEVEL (MG/DL)	DURATION OF ANTIHYPERLIPIDEMIC THERAPY (DAYS)
1048	A	Atromid	2000	636	41
1031	B	Clofibrate	2870	815	77
1066	B	Atromid-S	3570	626	126
2030	C	Lopid	1762	877	50
2020	D	Lopid	2568	1821	56
2031	D	Lopid	2085	1392	51

Source IND 43719 serial 409 vol 1 Table 13 and fax dated 3/11/98

Cholesterol

The applicant reports that patients in all treatment groups experienced increases in cholesterol levels from. For arms A and B the mean increase peaked at week 30 with an approximate increase of 98 mg/dL (arm B) and for arms C and D the mean increase peaked at week 8 with an approximate increase of 99 mg/dL (arm D). Table 3.4.7.4.1.7.1.D. summarizes the percent of subjects with cholesterol values > 240 mg/dL and > 300 mg/dL.

Table 3.4.7.4.1.7.1-D Cholesterol Abnormalities

	GROUP I		GROUP II		TOTAL
	Arm A	Arm B	Arm C	Arm D	Arms A-D
	RIT 400 BID/ SAQ 400 mg BID (n=35)	RIT 600 mg BID/ SAQ 400 mg BID (n=36)	RIT 400 mg TID/ SAQ 400 mg TID (n=33)	RIT 600 mg BID/ SAQ 600 mg BID (n=37)	(n=141)
Cholesterol Value > 240 mg/dL	21 (60%)	26 (72.2%)	18 (54.5%)	27 (73%)	92 (65.2%)
Cholesterol Value > 300 mg/dL	9 (25.7%)	11 (30.6%)	10 (30.3%)	10 (27%)	40 (28.4%)

Source: IND 43,718 serial 446

3.4.8. CONCLUSIONS

3.4.8.1.Efficacy

Based on an intent-to-treat analysis, the sponsor concluded that the proportions of patients with plasma HIV RNA < 200 copies/mL at week 48 were 74%, 68%, 55%, and 70% for treatment arms A, B, C, D, respectively. The median increase in CD4 cell counts for all groups was 128 cells/mm^3 at week 48. It is important to note that these results are confounded by alterations in dose and addition of other antiretroviral. It is noteworthy that a substantial proportion of patients receiving only dual protease inhibitor therapy was able to sustain virologic suppression. In arm A, 20/35 (57%) patients who had not added NRTIs had HIV RNA values < 200 copies/mL at week 48. Some of the patients who had added NRTIs were below the limit of assay quantification at the time; therefore, a still larger percentage may have responded successfully to dual protease inhibitor therapy alone.

3.4.8.2. Safety

It appears that treatment with ritonavir 400 mg BID and saquinavir 400 mg BID was generally well tolerated throughout the 48-week study period. Treatment with higher doses of ritonavir or saquinavir resulted in more frequent dose reductions/interruptions and discontinuations due to adverse events.
The most common adverse events seen during the trial were diarrhea (92%), asthenia (62%), nausea (62%), circumoral paresthesia (83%), lymphadenopathy (50%), and peripheral paresthesia (45%).

A total of 29 serious adverse events were reported in 16 patients through week 48 of this study. Four of the serious adverse events resulted in premature discontinuation from the study. There were no deaths at the time of database closure for the 48-week analysis.

A total of 35 patients withdrew from study prior to week 48. In FDA's analysis, 31 patients withdrew from the study due to adverse events. The majority of these patients had an ongoing or unresolved adverse event such as diarrhea, nausea, fatigue, or circumoral paresthesia at the time of discontinuation from study drug.

The majority of the laboratory abnormalities were related to increases in SGPT/SGOT, GGT and triglycerides. Patients who were randomized to receive ritonavir/saquinavir 600 mg BID and had underlying hepatic disease experienced the highest incidence of elevated liver function tests. All treatment regimens demonstrated statistically significant increases over baseline in triglyceride levels that persisted throughout the 48-week treatment period. Sixteen patients developed grade 3 or 4 (> 1500 mg/dL) elevations in triglyceride levels. Six patients had experienced an increase in triglycerides of greater than 2000 mg/dL and one patient had an increase in triglycerides of greater than 3000 mg/dL. In this study, there were no cases of hypertriglyceridemia-associated pancreatitis and no patients discontinued study treatment for elevated triglycerides. It is important to note that these findings are difficult to interpret because a number of patients had dose reductions during the study.

4.0 INTEGRATED SUMMARY OF EFFICACY

Study 247 unequivocally demonstrated that treatment with ritonavir delayed AIDS disease progression and death in patients with AIDS. Longer-term follow-up data out to 48 weeks showed a continued survival benefit for those patients who were initially randomized to ritonavir compared to placebo. This was apparent even after patients randomized to placebo were permitted to switch to open-label ritonavir.

Study 245 demonstrated that ritonavir produced superior virologic and immunologic responses than that of ZDV in less advanced, antiretroviral naïve, HIV-infected patients. These differences were observed out to 48 weeks. However, a large proportion of patients discontinued treatment in this study primarily due to intolerability of the study drug regimens. The largest number of discontinuations occurred among patients randomized to ZDV plus ritonavir. This probably accounted for the poorer performance of the combination arm compared to the ritonavir monotherapy arm. The capsule formulation of ritonavir together with dose escalation and staggering initiation of therapy with ZDV has helped with tolerability in other trials. However, it is clear that 600 mg bid of ritonavir is not well tolerated, as such it may not be a preferred regimen among available protease inhibitors. It should be noted that the treatment regimens in study 245, monotherapy/dual therapy, are no longer considered to be appropriate.

Study 462, although relatively small and uncontrolled, showed that a substantial proportion of HIV-infected patients receiving dual protease inhibitor therapy alone maintained virologic suppression below the assay limit at 48 weeks. This was observed with ritonavir doses of 400 mg bid (less than the approved dose). In addition, at 48 weeks, the RTV 400 bid/SQV 400 bid regimen (arm A) produced a similar virologic response as the RTV 600 mg bid/SQV 400 (arm B); however, the study was underpowered to conclude "equivalance" of these two regimens. In this study ritonavir doses of 400 mg bid appeared to be better tolerated than 600 mg bid, and, in fact, many patients initially assigned to 600 mg bid dose reduced to 400 mg bid.

The limitations of study 462 have been discussed with Abbott. In the future they have agreed to provide a report of a Danish study which evaluated RTV 400 bid plus SQV 400 mg bid versus RTV 600 mg bid or IDV 800 mg tid, all administered with the background of NRTIs. This study may help to further characterize the efficacy of dual protease therapy in relationship to more standard treatment with single protease inhibitors in combination with NRTIs.

In conclusion, the studies included in this traditional approval submission confirm that ritonavir is efficacious for both advanced and less advanced HIV-infected patients in studies conducted out to 48 weeks and beyond. This was demonstrated using clinical endpoints for patients with AIDS and virologic and immunologic markers for less advanced patients. Despite its demonstrated efficacy, ritonavir 600 mg bid may not be considered a preferred initial treatment because of its poor tolerability and overall safety profile, as discussed below.

5.0 INTEGRATED SUMMARY OF SAFETY

Additional and longer-term safety data included in this submission are similar to that provided in the original NDA. Many patients cannot tolerate full doses (600 mg bid) of ritonavir, especially when given as the oral solution or initiated at full doses with drugs with similar toxicities. According to study 462, ritonavir 400 mg bid in combination with saquinavir was better tolerated than ritonavir 600 mg bid in combination with saquinavir. In this study a substantial number of patients dose receiving ritonavir 600 mg bid reduced the ritonavir dose to 400 mg bid when used in combination with saquinavir.

The major toxicities of ritonavir, which include gastrointestinal toxicities, various paresthesias, liver toxicity, and lipid abnormalities, generally occur early in the course of treatment. In this submission, no new adverse events were identified that had not been previously identified in the original NDA or subsequent labelling supplements. However, several cases of pancreatitis with associated hypertriglyceridemia were identified in this submission and in postmarketing reports. These reports are summarized in section 5.1. Pancreatitis associated with hypertriglyceridemia will also be addressed in the updated package.

This submission also included further characterization of triglyceride and cholesterol abnormalities. If one considers triglyceride levels of 800 mg/dL as a possible threshold for medical intervention, then approximately 18% of individuals participating in studies #245 and #462 (ritonavir/saquinavir study) and one-third of the individuals in study #247 exceeded this threshold. If one considers cholesterol levels of 240 mg/dL as a possible threshold for medical intervention, then 18% and 25% of individuals receiving ritonavir in studies #245 and #247 exceeded this threshold and nearly two-thirds (60%) of individuals receiving ritonavir/saquinavir in study #462 exceeded this threshold. From the studies submitted it appears that the combination or ritonavir and saquinavir may be synergistic at increasing cholesterol. The combination did not appear to have the same degree of synergistic effect on

triglycerides. More safety data for ritonavir and saquinavir, especially with respect to lipid abnormalities are needed. Given the substantial increases in cholesterol and triglycerides, sections 5.1 and 5.2 below address the frequency of pancreatitis and the potential risk for myocardial infarction, respectively. In addition section 5.3, addresses the frequency of hepatotoxity with ritonavir and ritonavir/saquinavir regimens

5.1 Pancreatitis
Since ritonavir is known to cause substantial increases in triglycerides, a plausible causal mechanism for ritonavir-induced pancreatitis exists. In study 245, there were no cases of pancreatitis. During the entire study period of study 247, which enrolled patients with advanced AIDS (median CD4 approximately 20 cells), the overall frequency of pancreatitis was 1.6% (16 cases) and appeared to be less than that reported in the didanosine package insert (range 1-7%, adult studies, 3% pediatric studies). During the double blind period of study 247, there were four cases (0.7%) of pancreatitis among patients receiving placebo and 3 cases among patients receiving ritonavir. In study 432, which included patients rolling over from studies 245 and 247 (as well as other smaller studies), there were 5 cases of pancreatitis (0.6%). Three of the five were receiving ddI concomitantly. Also, three of the five cases reported large elevations of triglyceride levels 1320, 2780 and 1894 mg/dL. In study 462, in which less advanced patients received ritonavir in combination with saquinavir, there were no cases of pancreatitis. Thus, it appears that patients with more advanced disease may be at increased risk for pancreatitis, which has been observed for HIV in general.

During review of this application, the division requested that the applicant evaluate postmarketing reports describing pancreatitis. There were 32 reports of pancreatitis in the Norvir postmarketing database derived from spontaneous (n=25) and study (n=7) sources from 3/01/96-6/30/98. Four of the 32 cases resulted in death. Seven cases occurred among patients reporting use of ritonavir and saquinavir. Abbott reports that 13 (41%) of these 32 reports documented concomitant hypertriglyceridemia. The median triglyceride level in the setting of pancreatitis for these 13 cases was 2155 mg/dL (range: 365-7972). Due to incomplete reporting this is likely an underestimate of the number of cases of pancreatitis and the number of cases of pancreatitis with hypertriglyceridemia. Although Abbott states that hypertriglyceridemia has been reported in HIV infected subjects prior to the use of protease inhibitors, the reported increases were not nearly as profound as that associated with use of ritonavir. These reports indicate that ritonavir induced hypertriglyceridemia may lead to pancreatitis. Patients with advanced HIV are probably at increased risk.

5.2 Myocardial Infarction
Even if the observed increases in lipid levels associated with the use of ritonavir or ritonavir and saquinavir were associated with increased cardiovascular risk, including MI, it is unlikely that a signal would be identified in these studies of relatively short duration. As expected, among studies 245, 247, 432, and 462, there were only 3 reports of MI. In addition, there have been ten reports of myocardial infarction during the postmarketing period. Five of these reports mentioned possible alternative etiologies including underlying cardiac disease and anabolic steroid use. The

remaining five cases include 3 reports which provide no EKG or cardiac enzyme values. One report did state "triglycerides increased". Given the nature of these reports, it is difficult to attribute these events to ritonavir therapy. Large, long-term cohort studies will be needed to resolve this issue.

5.3 Hepatotoxicity

Grade 3 or 4 elevations in transaminases occurred in about 7-8% of individuals receiving ritonavir 600 mg bid. Risk factors for elevations in transaminases were: history of liver disorder, Hep B S-Ag positivity, Hep C Ab positivity, and low body weight (possibly indicating advanced disease). In addition 21% of patients receiving saquinavir 600 mg bid in combination with ritonavir in study 462 had grade 3 or 4 elevations in transaminases. In study 462 treatment arms in which saquinavir 400 mg bid was administered with ritonavir 400 mg bid or 600 mg bid, the frequency of transaminase elevations was similar to that observed for ritonavir 600 mg bid (without saquinavir) in other studies.

LABELING

The following labeling changes were negotiated:

CLINICAL PHARMACOLOGY

- Update Table 2: Effects of Co-administered Drug on Ritonavir Plasma AUC and C_{max} and Effects of Ritonavir on Co-administered Drug Plasma AUC and C_{max}

INDICATIONS

- delete " _____ from the indication statement

Description of Clinical Studies

- update data on efficacy through the end of studies 245, 247 and 432; and
- ____

CONTRAINDICATIONS

- revise protease inhibitor class labelling statements

WARNINGS

- Include a statement describing post-marketing adverse event reports of drug interactions with ritonavir and _____
- Include a statement regarding observed cases of pancreatitis with and without hypertriglyceridemia

PRECAUTIONS: Drug Interactions

- Include information on indinavir, ketoconazole, methadone, and rifabutin
- Revise Table 3: Predicted Effects on Drugs Co-administered with Ritonavir

ADVERSE REACTIONS

- update safety information from longer-term follow-up

DOSAGE AND ADMINISTRATION

- Include information on the dosages of saquinavir and ritonavir when used in combination

PHASE 4 COMMITMENTS

RECOMMENDED REGULATORY ACTION:

Based on the data submitted by Abbott Laboratories in support of fulfilling the accelerated approval commitments, the Division of Antiviral Drug Products has concluded that the accelerated approval for patients with less advanced HIV-1 disease may be converted to traditional approval.

Jeffrey Murray, M.D., M.P.H.
Medical Officer Team Leader

Kimberly Struble, Pharm.D.
Regulatory Review Officer

Concurrence:
HFD-530/DivDir/Jolson

cc:
Original NDA 20-659 and 20-680
Division File
HFD-530/RRO/Struble
HFD-530/MO/Murray
HFD-530/CSO/Lynche
HFD-530/Stat/Flyer, Hammerstrom