CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20828

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	20-828
APPLICANT:	Hoffmann-La Roche Inc.
NAME OF DRUG:	Saquinavir
INDICATION:	For use in combination with other antiretroviral agents in the treatment of HIV infection when therapy is warranted
DOCUMENTS REVIEWED:	Preliminary Report on Efficacy and Safety
MEDICAL INPUT:	HFD 530: Tan Nguyen, M.D.

A: Introduction

Hard geltin capsule formulation of saquinavir (SQV-HGC) has been approved for the treatment of HIV infection. However, the bioavailability of SQV-HGC is quite low and soft geltin capsule of saquinavir (SQV-SGC) with a substantially better bioavailability was developed. This submission is for the approval of SQV-SGC. The pivotal clinical trial NV15355 compared the treatment effects of SQV-SGC vs. SQV-HGC in combination with two nucleoside antiretroviral (NRTI) drugs in treatment naïve patients.

B: Study Design

Study NV15355

Protocol NV15355D: "A randomized, parallel arm, comparative, open label, multicenter study of the activity and safety of two formulations of saquinavir in combination with two nucleoside antiretroviral drugs in treatment naïve patients".

The planned sample size was 140 patients. Patients were to be equally randomized into two treatment groups with stratification by pre-baseline plasma HIV RNA levels (≥20,000 or 5,000-20,000). Each stratum would have at least 25% of the total patients enrolled.

A. SQV-HGC 600 mg TID + 2 new NRTIs
B. SQV-SGC 1200 mg TID + 2 new NRTIs

The primary outcome measure was the AUCMB for plasma HIV-1 RNA at Week 16. Patients were to be assessed at Week 4, 8, 12 and 16. Time windows for efficacy parameters were ±14 days around pre-specified visiting dates. The primary comparison of the two treatment groups was to be performed using the analysis of covariance method. The model would include Region, Treatment, HIV RNA stratum and CD4 cell counts at entry.

Secondary outcome measures included:

Time to virologic relapse
Proportion of virologic responders
Proportion of virologic relapsers
Proportion of virologic failures
Proportion of patients below quantification
CD4, CD4%, CD8, CD8%, absolute lymphocyte counts

The sample size was based on a difference of 0.6 $\log_{10}$ and standard deviation of 0.9 $\log_{10}$ at Week 16 for AUCMB metric for HIV-1.RNA at significance level 0.05 with 90% power. Dropout rate was assumed to be 5%.

Intent-to-treat population was to be used for the primary analysis.

The primary and secondary analyses was to be conducted at Week 16. The trial would last for 48 weeks beyond the date the last patient enrolled. Patients was to be offered the possibility of switching SQV formulations after 16 weeks of treatment.

C: Applicant's Results

Study NV15355

179 patients were randomized into two treatment arms. Of them 171 took medication, and 24 withdrew from study before database closure for the 16 week analysis. The following table provides the distribution of subjects randomized by treatment and follow-up status. The major reasons for premature withdrawal from treatment were adverse events, withdrawal of consent and loss to follow-up. Withdrawals due to adverse events occurred more frequently in SQV-SGC than was in SQV-HGC group ($p<0.01$). There were no apparent differences between the two treatment arms in number of withdrawals due to other causes. The majority of withdrawals occurred in the first 8 weeks.

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Disposition of Patients Entered Into the Study

	SQV-HGC	SQV-SGC
Number enrolled and randomized	86	93
Number taking at least one dose of study medication	81	90
Number withdrew Prematurely	7	17
Withdrew due to:		
Adverse events	1	9
Lost to follow-up	5	1
Withdrew consent	1	5
Administrative	0	1
Protocol violation	0	1
Withdrew during:		
Week 1-4	3	9
Week 5-8	2	5
Week 9-16	2	3

Source: Figure 1, Table 2 and 4, page 10, 11 and 14 of Preliminary Report for NV15355

Analyses were conducted for the intent to treat population which includes all patients who received at least one dose of study medication, and for the standard population which excludes patients with protocol deviation/violations and patients withdrew prematurely. The following table summarizes the distribution of patients in the two populations:

Total Number of Patients in Analysis Populations

	SQV-HGC	SQV-SGC
Total number in the intent to treat population	81	90
Total number in the standard population	70	71

Source: Table 2, page 11 of Preliminary Report for NV15355

Baseline demographics were similar in the two treatment groups (Source: Table 3 of Preliminary Report, Page 12). Baseline HIV RNA levels were also comparable (Source: Table 5, Page 15 of Preliminary Report). Baseline CD4 lymphocyte count was somewhat higher (p-value = 0.21) in the SQV-SGC group (mean value 447.5cells/mm^3) than in the HGC group (mean value of 408.0 cells/mm^3).

HIV RNA

HIV RNA was evaluated using the Amplicor assay (level of quantification 400 copies/mL to 750,000 copies/mL). Values below 400 copies/mL were set to 400 copies/ml while values above 750,000 copies/mL were set to 750,000 copies/mL. Measurements based on ultra sensitive assay which has quantification range 50 copies/mL - 30,000copies/mL was also obtained but only analyses based on Amplicor assay were presented.

The table below summarizes the change from baseline for $\log_{10}$ (HIV RNA):

Summary of $\log_{10}$ (HIV RNA) - Change From Baseline

	SQV-HGC			SQC-SGC		
Visit	N	Mean (Std Dev)	Median (interquartile range)	N	Mean (Std Dev)	Median interquartile range
Week 4	74	-1.80 (0.49)	-1.83	83	-1.74 (0.54)	-1.84
Week 8	71	-1.83 (0.57)	-1.87	79	-1.92 (0.60)	-2.02
Week 12	75	-1.72 (0.63)	-1.77	78	-1.96 (0.67)	-1.99
Week 16	69	-1.56 (0.63)	-1.58	75	-1.96 (0.66)	-1.99

Source: Table 6, page 16 of Preliminary Report for NV15355

A drop of HIV RNA level (around 1.8) was observed in the first 4 weeks in both treatment groups. This decrease was maintained or improved in SGC group through Week 16. In HGC group there was a rebound of HIV RNA level after Week 8.

The efficacy parameters based on HIV RNA levels include AUCMB and proportion of patients below quantification limit at Week 16.

(1) AUCMB at Week 16

AUCMB for each patient was calculated by the following:

$$AUCMB = AUC_t/t - Baseline$$

where AUC_t is the area under the $\log_{10}$ (HIV RNA) curve up to time t, and t is the number of days within the 16 weeks time period.

All available information up to Week 16 or at least up to the last available visit (t) was used to calculate the AUC using the trapezoidal rule. Missing intermediate values was ignored: this is equivalent to the replacement of missing values by the mean of the neighboring visits. There appears to be little difference between the two arms in average AUCMB. The table below summarize this information:

Summary of AUCMB for $\log_{10}$ (HIV RNA) at Week 16

SQV-HGC			SQC-SGC		
N	Mean (Std Dev)	Median (interqartile range)	N	Mean (Std Dev)	Median interqartile range
78	-1.49 (0.43)	-1.53	86	-1.57 (0.52)	-1.66

Source: Table 8, page 20 of Preliminary Report for NV15355 and review's calculation

The protocol-specified analysis for AUCMB at Week 16 is analysis of covariance (ANCOVA) adjusting for the effects of region, pre-baseline HIV RNA stratum and baseline CD4 lymphocyte count. No statistically significant difference was observed (p=0.1929). The analysis results are presented below:

ANCOVA results for AUCMB at Week 16

Effect	p-value	Least Square Mean (95% CI)
SQV-SGC vs. SQV HGC	0.1929	-0.09 (-0.23, 0.05)
SQV-HGC		-1.29 (-1.41, -1.17)
SQV-SGC		-1.38 (-1.50, -1.27)

Source: Table 14, page 28 of Preliminary Report for NV15355

(2) HIV RNA Below Level of Quantification

The Week 16 (±2 weeks) HIV RNA levels for all patients randomized and taking at least one dose of study medication (ITT population) is summarized in the following table:

Patient HIV RNA Status at Week 16

Treatment	Sample Size	# Below Quantification (%)	# Unknown (%)
SQV-HGC	81	30 (37.0%)	12 (14.8%)
SQV-SGC	90	60 (66.7%)	15 (16.7%)

Source: Table 16 and 18, page 29 and 30 of Preliminary Report for NV15355

With all unknowns classified as failures (above level of quantification), 66.7% of patients in SQV-SGC treatment arm achieved viral load below level of quantification compared to 37.0% in the SQV-HGC treatment arm. Chi-Square test yielded p-value 0.001, statistically significant at level 0.05. However, it is not clear if the randomization stratification variables were incorporated into this test.

CD4 Lymphocyte Cell Count

The table below summarizes the change from baseline for CD4 counts:

Summary of CD4 counts - Change From Baseline

	SQV-HGC			SQC-SGC		
Visit	N	Mean (Std Dev)	Median (interqartile range)	N	Mean (Std Dev)	Median interqartile range
Week 4	76	63.1 (130.0)	69.5	80	34.3 (138.9)	36.5
Week 8	71	75.2 (118.3)	60.0	77	51.4 (155.0)	79.5
Week 12	74	66.9 (114.3)	74.0	78	64.5 (145.3)	63.0
Week 16	70	114.7 (122.1)	103.3	73	96.5 (151.9)	85.0

Source: Table 12, page 25 of Preliminary Report for NV15355

Increases in the mean CD4 lymphocyte cell count up to week 16 occurred in both treatment arms. No statistical comparison were provided in the Preliminary Report.

AUCMB for CD4 counts is summarized below.

Summary of AUCMB for CD4 Count at Week 16

SQV-HGC			SQC-SGC		
N	Mean (Std Dev)	Median (interqartile range)	N	Mean (Std Dev)	Median interqartile range
79	63.6 (84.5)	72.7	85	43.9 (101.9)	57.3

Source: Table 13, page 27 of Preliminary Report for NV15355

Again, no statistical comparison was provided in the Preliminary Report. T-test based on the observed mean and standard deviation given in the table above yielded two-sided p-value 0.1766.

D: Reviewer's Comments and Analyses

Since at the time the protocol was written, there was no consensus on which of the many possible measures based on HIV RNA level should be used as the primary efficacy variable, and FDA and the sponsor chose AUCMB. Since that time consensus have developed and suppression of viral RNA to below quantification has itself become a goal of therapy. Therefore, for this review both AUCMB and proportion below quantification will be treated as the primary efficacy variables.

The reviewer's calculation of AUCMB was based on the actual days since randomization, including all observations up to Week 18, with baseline average treated as if it were observed on

Day 0. This is different from the sponsor's calculation in that the sponsor used the observations upto 1000 days from the end of the trial.

1) AUCMB at Week 16

AUCMB is a measure of the average decrease of $\log_{10}$(HIV RNA) levels while patients were on the study medication. It was affected by the dropout pattern and missing observations. It was also affected by the precision and the detection limit of the instrument used for the measurements. The sponsor's analysis was based on the Amplicor assay which has a low detection limit of 400 copies/mL and has been validated. Since the sponsor also measured the HIV RNA levels using the ultra sensitive assay which has a low detection limit of 50 copies/mL, a mixed measure of HIV RNA levels can be derived to utilize this additional information and analyses can be conducted on this new measure. Since a large proportion of patients (37% in HGC and 67% in SGC) had HIV RNA levels below 400 copies/mL at Week 16, the mixed measure may provide hopefully a more sensitive comparison between the two treatments. Note since the two measures are unlikely to be the same and such a mixed measure will inevitably introduce biases. The analyses based on this mixed measure is viewed only as supportive.

The mixed HIV RNA levels can be defined as following: The mixed HIV RNA level equals to the RNA level based on Amplicor assay unless it is below the detection limit (400 copies/mL). when the observed HIV RNA level is below the detection limit, the mixed RNA level is the minimum of 400 and RNA level based on ultra sensitive assay. This measure is mainly based on the amplicor RNA level, the RNA level derived from ultra sensitive assay is used only when this information is not available. To verify the sponsor's results, the sponsor's analysis was repeated using the mixed HIV RNA levels.

The table below summarizes the change of mixed HIV RNA levels from baseline. Bootstrap 95% confidence intervals for median were generated with 1000 re-samplings. The 95% confidence interval for mean was based on normal approximation. Note even with the ultra sensitive assay, 23.5% of patients in HGC group and 36.7% in SGC group had RNA levels below quantification (50 copies/mL) and their values were set to 50 copies/mL. Such maneuver will inflate the mean but will affect the median little.

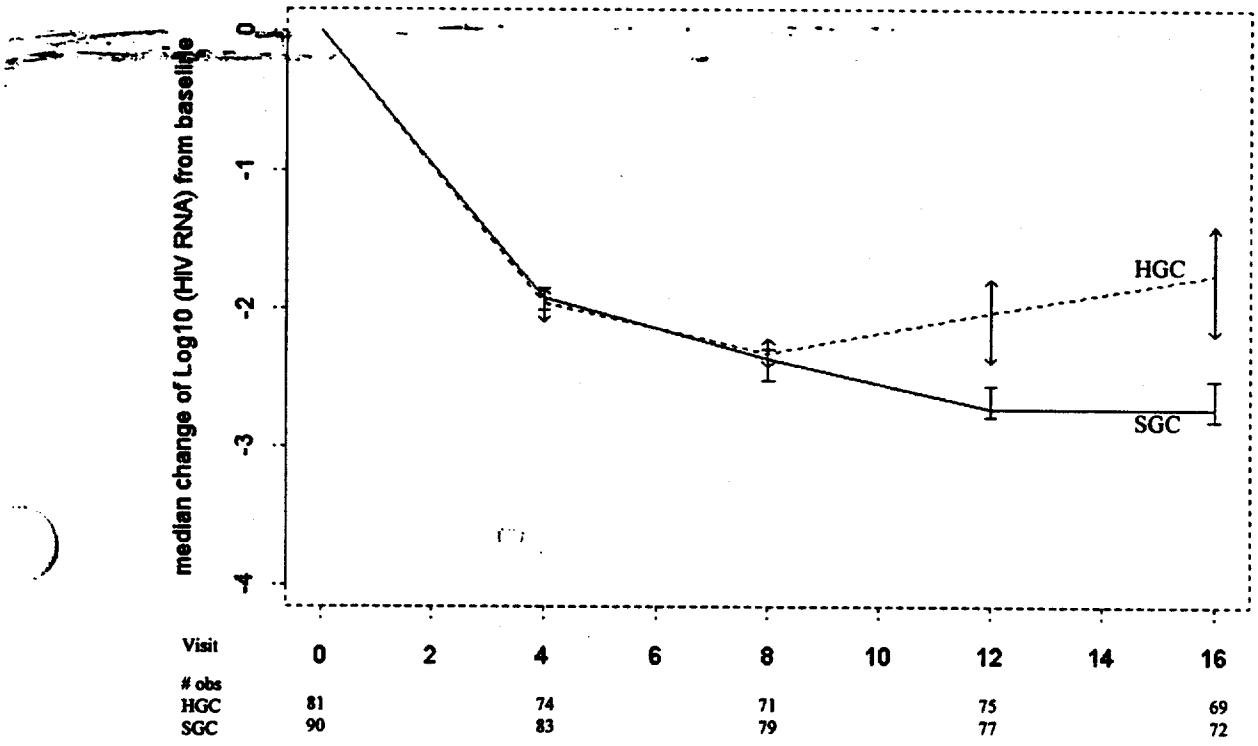
Change of Log10(HIV RNA) Levels from Averaging Baseline Using Mixed HIV RNA Measures

Visit	treatment	size	mean (sd)	95% CI	median	Quartiles	95% CI*
4	HGC	74	-1.923(0.5026)	(-2.0375, -1.8085)	-1.9554	(-2.2006, -1.6926)	(-2.0911, -1.8503)
	SGC	83	-1.8714(0.5759)	(-1.9953, -1.7475)	-1.9136	(-2.2348, -1.7181)	(-2.003, -1.8508)
8	HGC	71	-2.1614(0.7064)	(-2.3257, -1.9971)	-2.3199	(-2.6126, -1.7292)	(-2.4141, -2.2136)
	SGC	79	-2.2737(0.6914)	(-2.4262, -2.1212)	-2.3591	(-2.6442, -2.1163)	(-2.519, -2.2862)
12	HGC	75	-2.0383(0.8603)	(-2.233, -1.8436)	-2.0197	(-2.6625, -1.4034)	(-2.3839, -1.7799)
	SGC	78	-2.4983(0.7741)	(-2.6701, -2.3265)	-2.7231	(-2.955, -2.2689)	(-2.7817, -2.552)
16	HGC	69	-1.8593(0.9084)	(-2.0736, -1.6450)	-1.7541	(-2.5471, -1.1423)	(-2.1949, -1.3978)
	SGC	75	-2.5241(0.8295)	(-2.7118, -2.3364)	-2.7245	(-3.0852, -2.0942)	(-2.8083, -2.519)

*Bootstrap with 1000 repetitions

The plot below plots the median change of mixed HIV RNA levels and the corresponding bootstrap 95% confidence interval.

Plot of the Change of Mixed HIV RNA Levels and 95% Confidence Intervals



It appears that the change of HIV RNA levels were different at Week 12 and 16. Cochran-Mantel Haenszel (CMH) tests with stratification by the pre-baseline HIV RNA level (≥20,000 or 5,000-20,000) yielded p-values < 0.001 at Week 12 and Week 16. Caution: since there were more missing observations at Week 12 (6 in HGC vs. 13 in SGC) and Week 16 (12 in HGC and 18 in SGC) in SGC group, it is not clear how these missing observations should be included in the analysis. Without them the estimates are likely to be biased.

The primary endpoint, AUCMB16, was calculated based on the mixed RNA levels and the results are summarized in the table below.

Summary of AUCMB for $\log_{10}$ (HIV RNA) using mixed RNA levels at Week 16

SQV-HGC			SQC-SGC		
N	Mean (Std Dev)	Median (interqartile range)	N	Mean (Std Dev)	Median interqartile range
78	-1.71 (0.52)	-1.76	86	-1.87 (0.59)	-2.00

The protocol-specified analysis for AUCMB at Week 16 is analysis of covariance (ANCOVA) adjusting for the effects of region, pre-baseline HIV RNA stratum and baseline CD4 lymphocyte count. The analysis results is presented below:

ANCOVA results for AUCMB using mixed HIV RNA levels at Week 16

Effect	p-value	Least Square Mean (95% CI)
SQV-SGC vs. SQV HGC	0.0703	-0.16 (-0.3356, 0.0135)
SQV-HGC		-1.62 (-1.769, -1.465)
SQV-SGC		-1.78 (-1.924, -1.632)

It appears that there is marginal evidence that SQV-SGC is superior to SQV-HGC in reduction of HIV RNA levels at Week 16 from baseline.

2) Proportion below detection

5 of 86 patients randomized to SQV-HGC and 3 of 93 patients randomized to SQV-SGC did not take any medication. These patients were excluded in the sponsor's analyses. Since inclusion of these patients in the intent-to-treat population will usually favor SQV-SGC (for example, when these patients were classified as above the limit of detection), therefore in the calculations below these patients were excluded.

The patient status at Week 16 is summarized below.

Patient HIV RNA Status at Week 16

Treatment	Sample Size	# Below Quantification (%)	# Unknown (%)
SQV-HGC	81	30 (37.0%)	12 (14.8%)
SQV-SGC	90	60 (66.7%)	15 (16.7%)

Source: Table 16 and 18 and Appendix 3, page 29 and 30 and 64 of Preliminary Report for NV15355

The unknowns can be summarized below:

Drug (total)	Terminated Before Week 16 Evaluation					Completed Trial
	Lost to Follow-up	AE	Non-Cooperation	Administrative	Other Protocol Violation	but No Evaluation
HGC	5	1	1	0	0	5
SGC	1	7	5	1	1	0

With all unknowns classified as failures (above level of quantification), 66.7% of patients in SQV-SGC treatment arm achieved viral load below level of quantification compared to 37.0% in the SQV-HGC treatment arm. Chi-Square test yielded p-value 0.001, statistically significant at level 0.05.

To see if the analysis results for proportions below detection limit depend on the assumptions for the patients whose Week 16 HIV RNA level measures were unknown, the worst possible case is considered here. In this analysis all such patients are classified as above detection limit in SGC group while they are classified as below detection limit in the HGC group. The result is summarized in the following table:

Patient HIV RNA Status at Week 16

Treatment	Sample Size	# Below Quantification (%)	# Unknown (%)
SQV-HGC	81	42 (52.0%)	12 (14.8%)
SQV-SGC	90	60 (66.7%)	15 (16.7%)

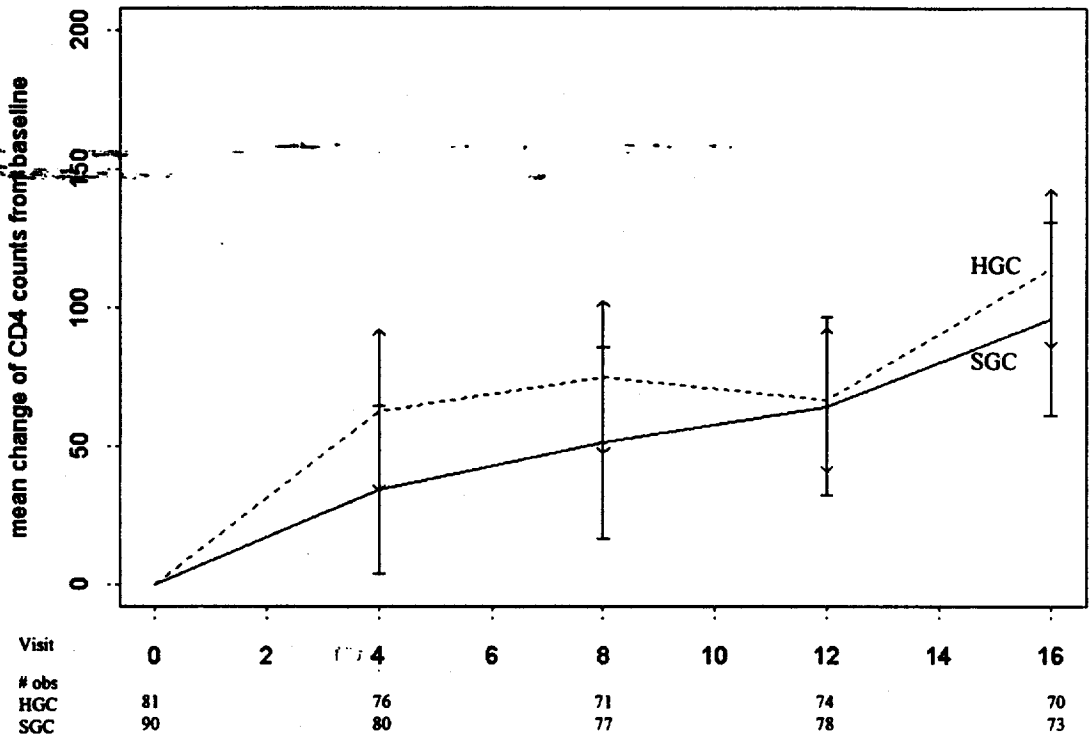
Source: Table 16 and 18, page 29 and 30 of Preliminary Report for NV15355

66.7% of patients in SQV-SGC treatment arm achieved viral load below level of quantification compared to 52.0% in the SQV-HGC treatment arm. Pre-baseline HIV RNA level-stratified-CMH test yielded p-value 0.05. Therefore there is evidence that SQV-SGC achieved a higher proportion of below detection than SQV-HGC even in this extreme case.

3) CD4 cell counts

The HGC and SGC groups differ little in the change of CD4 cell counts from baseline at each visit. The following plot depicts the mean CD4 cell counts observed at each visit and their 95% confidence intervals. Note all the estimates were based on the observed data. These estimates may be biased since they did not address how the missing data should be replaced.

Mean Change of CD4 Count from Baseline and its 95% Confidence Interval



AUCMB for CD4 was calculated the same way as for the AUCMB for Log10 (HIV RNA), which is slightly different from the sponsor's calculation. However, the difference between the sponsor's results differ little from the reviewers. The following table summarizes the results of the analysis of covariance for AUCMB of CD4 at Week 16, adjusted for pre-baseline RNA level, region, treatment and baseline CD4 counts.

ANCOVA results for AUCMB of CD4 at Week 16

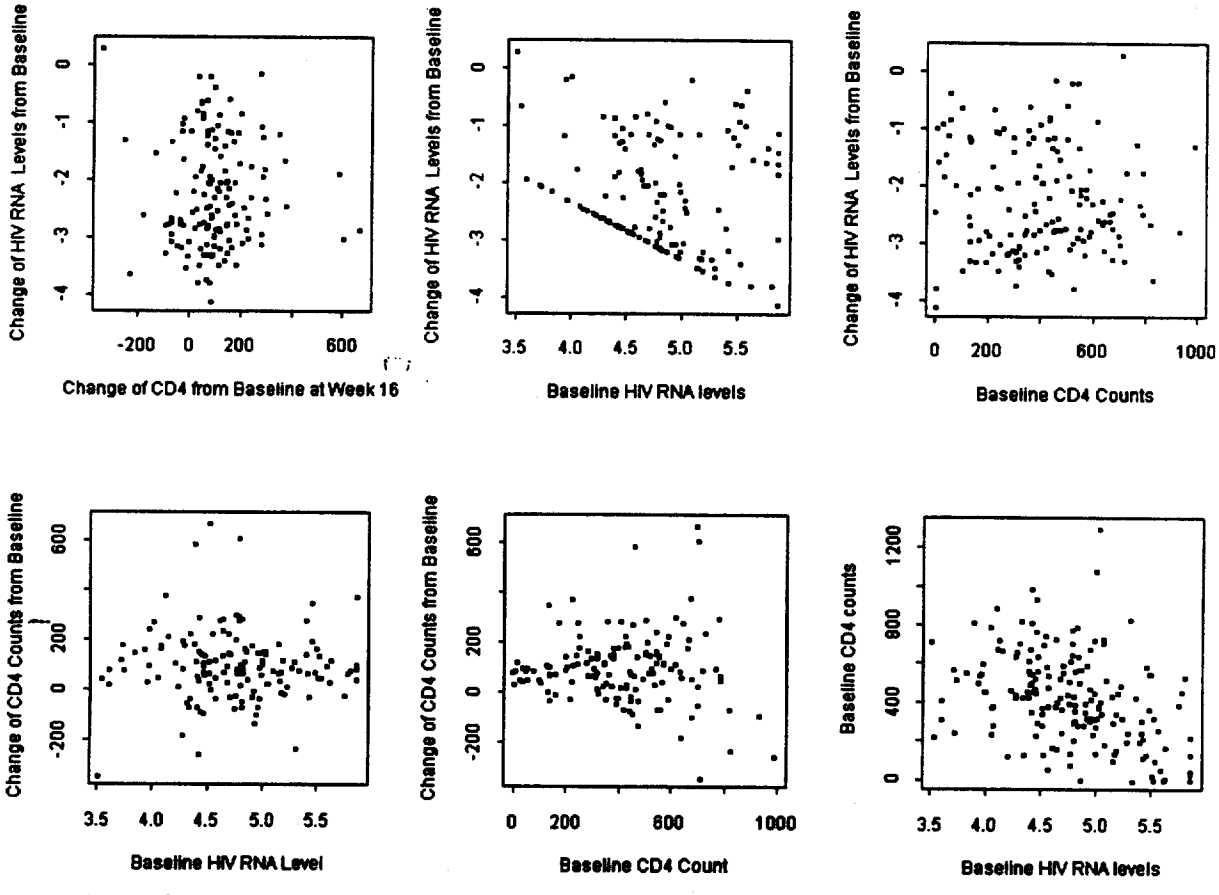
Effect	p-value	Least Square Mean (95% CI)
SQV-SGC vs. SQV HGC	0.3320	-13.89 (-42.08, 14.30)
SQV-HGC		62.24 (37.67, 86.81)
SQV-SGC		48.35 (24.69, 72.01)

Overall, no statistically significant difference in CD4 response was observed for the two treatment arms.

3) HIV RNA and CD4

As the two most widely used surrogate markers for measuring treatment effects of HIV infection, it is of interest to know how changes in one marker will affect the other one, and if baseline values of these variables are of interest in predicting the future outcome of the treatment.

Plots of Log$_{10}$ HIV RNA levels and CD4 counts at baseline, as well as changes from baseline at Week 16 were plotted against each other to examine the possible associations.



From these plots we see little evidence that baseline values of HIV RNA levels and CD4 counts affect the size of changes from baseline for the two efficacy marks. Further, little correlation were found for the CD4 count and HIV RNA level, both at baseline and for the change from baseline at Week 16.

E: Statistical Reviewer's Overall Assessment

Based on study NV15355, the following statistical conclusions can be drawn:

(1) There is no substantial evidence that SQV-SGC group had better response at Week 16 than SQV-HGC group as measured by AUCMB metric.

(2) A significantly higher percentage of patients in SQV-SGC group achieved viral load below 400 copies/mL than those in SQV-HGC group.

(3) There is little evidence that there is a difference between SQV-SGC group and SQV-HGC group in change of CD4 from baseline.

Greg Soon, Ph.D.
Mathematical Statistician

Concur: Dr. Flyer

cc:
Archival NDA20828
HFD-530
HFD-104/Ms. Sage (via teamlinks)
HFD-530/Dr. Birnkrant (via teamlinks)
HFD-530/Dr. Murray
HFD-530/Dr. Nguyen
HFD-530/Mr. Kelly
HFD-725/Dr. Flyer
HFD-725/Dr. Huque
HFD-725/Ms. Shores
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This review contains 13 pages.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20828

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DRAFT

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Reviewer : Prabhu Rajagopalan, Ph. D.
NDA : 20828.

TYPE : 1P
DRUG : Saquinavir (FORTOVASE ®)
FORMULATION : Soft gelatin capsule
APPLICANT : Hoffmann La-Roche

SUBMISSION DATES : 05-12-97, 05-22-97, 07-21-97, 07-28-97, 08-20-97, 08-27-97 and 10-02-97.
DRAFT REVIEW : 10-31-97
FINAL REVIEW :

BACKGROUND

Saquinavir is a protease inhibitor used in the treatment of HIV infection. The hard gelatin capsule (HGC) formulation of saquinavir mesylate (INVIRASE®) was approved by the Agency in December 1995. The recommended dosing regimen for INVIRASE® is 600 mg t.i.d. Due to the low bioavailability of saquinavir (~ 4%) from INVIRASE®, the Applicant has developed a soft gelatin capsule (SGC) formulation using saquinavir free base (FORTOVASE®). At the proposed recommended dose of 1200 mg t.i.d. of FORTOVASE®, after three weeks of treatment, saquinavir exposure is around eight to ten times greater than the exposure observed after administration of INVIRASE® at 600 mg t.i.d.

The Applicant performed a dose ranging study with saquinavir SGC to determine the proposed recommended dose. One core clinical trial (NV15182) was conducted with the SGC formulation and another core clinical trial (NV15355) is in progress. The safety study NV15182 was conducted in 442 HIV positive patients. These patients also received reverse transcriptase inhibitors along with saquinavir SGC. Study NV15355 compares the efficacy of saquinavir HGC and SGC treatments. 179 HIV infected and protease inhibitor treatment naïve patients are participating in this study and the Applicant has recently submitted the 16 week efficacy data. The above mentioned studies form the basis for the New Drug Application for FORTOVASE ®.

SYNOPSIS

The important features in the pharmacokinetics and disposition of saquinavir SGC and HGC formulations are presented in this synopsis. A detailed review begins on page 7. The Applicant provided these data on a continuos basis (from March to October 1997) and it was necessary to adopt an interactive approach in reviewing this NDA. The final study reports were reviewed individually and these reviews have been compiled into a review for this NDA.

ABSORPTION

The pharmacokinetics of saquinavir were highly variable following oral administration of saquinavir SGC. In 33 patients receiving 1200 mg t.i.d., mean C_{max} and AUC_8 values varied from 138 to 7757 ng/mL and 496 to 25034 ng.h/mL, respectively

after 1 week of treatment. At steady-state, the intra-subject and inter-subject variability in pharmacokinetic parameters (AUC and C_{max}) were approximately 60% and 80%, respectively.

Multiple dose pharmacokinetic data indicate greater than dose proportional increase in saquinavir exposure. The AUC increased by ~4 fold when the dose was doubled from 400 mg t.i.d. to 800 mg t.i.d. and increased by ~2 fold when the dose was increased by 50% from 800 mg t.i.d to 1200 mg. t.i.d..

Food was found to have a significant effect on the absorption of saquinavir. When compared to saquinavir administered under fasting condition, saquinavir AUC values were 6 to 7 fold greater under fed condition. Administration of an experimental soft gelatin capsule formulation of saquinavir with quadruple strength grape fruit juice, resulted in a 50% and 18% increase in AUC and C_{max} values, respectively.

HEALTHY SUBJECTS VERSUS PATIENTS

The pharmacokinetics of saquinavir SGC were significantly different in patients when compared to healthy subjects. At steady-state, the mean C_{max} and AUC_8 values were 1420 ng/mL and 4159 ng.h/mL, respectively in healthy subjects receiving 1200 mg t.i.d for 7 days. These values were approximately 2 fold greater in patients receiving the same dose. The mean C_{max} and AUC_8 were 2476 ng/mL and 8839 ng.h/mL, respectively. Comparison of data obtained from a single dose study and a multiple dose study indicate 80% accumulation upon multiple dosing in healthy male subjects. Such data are not available in patients.

RELATIVE BIOAVAILABILITY

The absolute bioavailability of saquinavir from SGC has not been assessed by the Applicant. The relative bioavailability of saquinavir from the SGC formulation, with respect to the HGC formulation, is approximately 330%. The Applicant has estimated the absolute bioavailability of saquinavir from the HGC formulation to be approximately 4%. These studies were submitted under NDA 20628.

BIOEQUIVALENCY

Formulations A01, A12 and A22 are clinical trial formulations of saquinavir SGC. The grade of an excipient, medium chain mono- and diglycerides, was the only difference between these formulations (See page 8). The Applicant noticed that the capsule fill had a tendency to gel upon storage and, therefore, developed a formulation containing . This formulation is the *proposed market formulation* and will be referred to as A24 (with imprint) and A27 (without imprint). A batch of A22 was considerably gelled soon after it was manufactured. This batch, referred to as A31, represents the worst case scenario in terms of gelling. The batch sizes of A22 and A31 were respectively.

According to the Applicant, the proposed market formulation was used in both the core clinical trials which support this NDA. In the 48 weeks *safety study NV15182*, the proposed market formulation was used in the clinic for approximately 35 weeks. A majority of the patients enrolled in this study received the proposed market formulation for a period of more than 26 weeks. Patients participating in the *efficacy study NV15355* received the proposed market formulation from the first day of treatment.

The Applicant performed three relative bioavailability / bioequivalence studies. The first study (WP15193) was performed to compare Formulations A22 and A24. Due to high variability in the pharmacokinetics of saquinavir, the stable isotope technique was used in bioequivalency assessments. Based on the protocol specified analysis[1], the two formulations were found to be bioequivalent.

The second study (WP15191) was conducted to compare Formulations A22, A31 and an experimental formulation A25. This study was also conducted using the stable isotope technique. According to the protocol specified analysis[1], the relative bioavailability of the gelled formulation A31 was 117% [90% CI: 99 -137] and 115% [90% CI: 93 - 141], based on RAUC and RC_{max}, respectively when compared to Formulation A22. Based on the unlabeled dose, the relative bioavailability of A31 was 100%. The Reviewer's opinion on the applicability of the stable isotope technique for saquinavir is presented in the review of this final study report.

The third study (WP15343) deals with A27 (liquid fill), A27 (gelled fill) and A31. The capsules used in the A27 (gelled fill) treatment were manufactured by a process which ensures gelling of capsule contents. The results of this study indicate, that despite gelling, the relative bioavailability of A27 (gelled fill) treatment was 106% [90% CI: 92 - 122] and 103% [90 - 117] based on AUC and C_{max}, respectively. In the case of A31, the relative bioavailability was 88% [90% CI : 76 -101] and 92% [90% CI: 81 - 105] based on AUC and C_{max}, respectively.

DISTRIBUTION

The Applicant has characterized the pharmacokinetics of saquinavir after intravenous administration and has conducted a mass balance study with ^{14}C–saquinavir. These studies were reviewed under NDA 20628. Information from INVIRASE® label is presented in this section and the metabolism and elimination section.

The mean steady state volume of distribution after intravenous administration of 12 mg of saquinavir was 700 L. The systemic clearance was high and averaged 1.14 L/h/kg after intravenous doses of 6, 36 and 73 mg. The mean residence time of saquinavir was 7 hours. Limited data indicate negligible saquinavir concentrations in the cerebrospinal fluid following oral administration of saquinavir. *In vitro* protein binding studies indicate that more than 97% of saquinavir is bound to plasma proteins in the concentration range 0.1 to 30 µg/mL.

METABOLISM AND ELIMINATION

In vitro studies indicate that the metabolism of saquinavir is mediated by cytochrome P450 3A4. In these *in vitro* studies, saquinavir was rapidly metabolized to mono- and di- hydroxylated inactive compounds. This isozyme is responsible for more than 90% of hepatic metabolism.

---

[1] The reference and test formulations were administered along with a formulation containing a stable isotope of saquinavir. The ratio of saquinavir AUC from the reference treatment to saquinavir AUC from the stable isotope formulation was calculated for all the subjects (RAUC). Similarly RAUC was computed for the test treatment. The two one-sided bioequivalency test was performed on the RAUC values to determine bioequivalency. In a similar fashion bioequivalency was determined for the C_{max} variable.

Following oral administration of 600 mg of ^{14}C-saquinavir, 88% and 1% of the orally administered radioactivity was recovered in feces and urine, respectively within five days of dosing. In this study, 13% of circulating radioactivity in plasma was attributed to unchanged drug and the remainder to saquinavir metabolites. Following intravenous administration of ^{14}C-saquinavir, 81% and 3% of radioactivity was eliminated in feces and urine, respectively within 5 days of dosing. After intravenous administration, 66% of the radioactivity was attributed to unchanged drug and the remainder to saquinavir metabolites. These data suggest that saquinavir undergoes extensive first-pass metabolism.

DRUG INTERACTIONS

Several drug interaction studies were performed by the Applicant with FORTOVASE®. These studies include evaluation of interaction effects with other protease inhibitors such as ritonavir, nelfinavir and indinavir. The Applicant also studied interaction effects with clarithromycin and terfenadine.

Ritonavir had a profound effect on the pharmacokinetics of saquinavir. Following concomitant administration of saquinavir SGC (400 mg b.i.d) and ritonavir (400 mg b.i.d) to healthy volunteers, mean saquinavir AUC value was seven fold greater than the mean value observed after administration of saquinavir SGC (800 mg b.i.d) alone, probably due to inhibition of CYP3A4 by ritonavir. Preliminary data indicate that saquinavir did not have a clinically significant effect on the pharmacokinetics of ritonavir.

Concomitant administration of a 1200 mg single dose of saquinavir SGC and *indinavir or nelfinavir* 'at steady-state' resulted in a five fold increase in saquinavir exposure. Single dose of saquinavir did not appear to have a significant effect on the exposure of indinavir or nelfinavir.

The drug interaction study with *clarithromycin* indicates that concomitant administration of saquinavir and clarithromycin increases the plasma levels of both the drugs. Saquinavir AUC increased by approximately 175%, while a 45% increase and a 25% decrease was noted in the AUC of clarithromycin and 14-OH clarithromycin metabolite, respectively.

Concurrent administration of saquinavir and *terfenadine* resulted in a five fold increase in terfenadine AUC and two fold increase in terfenadine acid metabolite AUC. The mean QTc interval following concomitant administration increased by 6%. In light of these findings, it is recommended that terfenadine should not be administered with saquinavir.

ADDITIONAL STUDIES

The Applicant performed three studies to determine the drug interaction effects between saquinavir and ketoconazole, erythromycin and rifampin. The protocol was designed to allow patients receiving saquinavir SGC for more than 24 weeks to participate in the drug interaction study. Upon completion of the study, the Applicant discovered that plasma saquinavir levels in the control arm of these interaction studies were 50% lower when compared to levels obtained after 1 to 3 weeks of treatment in a previous study.

Although a specific reason for lower plasma levels is not clear at this time, the Applicant speculates that this may be due to physiological changes in the gastrointestinal tract. It appears that changes in intestinal permeability, transport related processes and / or modification of pre-systemic metabolism during saquinavir treatment may be responsible for lower plasma concentrations following long term saquinavir therapy. In this context, it should be noted that the plasma saquinavir levels (following administration of both saquinavir HGC and saquinavir SGC) in healthy volunteers is 50% of the levels seen in HIV infected patients.

The Applicant has proposed to obtain complete plasma concentration time profiles from patients participating in two ongoing clinical trials to determine the time course of decrease in plasma saquinavir levels.

SPECIAL POPULATION

The pharmacokinetics of saquinavir SGC have not been investigated in patients with hepatic or renal impairment. Although the Applicant has not formally investigated gender effect, comparison of available data does not indicate any gender difference in the pharmacokinetics of saquinavir. The pharmacokinetics of saquinavir have not been assessed in the pediatric (<16 years) or geriatric (>65 years) patient population.

PK-PD CORRELATION

The Applicant has attempted to correlate Week 8 response measurements such as AUCMB (Area Under the Curve Minus Baseline of HIV RNA) and peak reduction in HIV RNA from baseline to AUC and C_{min} that were obtained during Week 1 and 3 of treatment. According to the Applicant, the data were best described by the E_{max} model. 400 mg, 800 mg and 1200 mg t.i.d. were the three doses investigated in the above study. Based on the results of this study, 1200 mg t.i.d. was chosen for all other studies.

PK-DEMOGRAPHIC VARIABLE CORRELATION

Based on available data, the Applicant was not able to demonstrate a correlation between age, weight or baseline CD_4 count and either C_{max} or AUC.

RECOMMENDATION

The pharmacokinetic studies submitted under NDA 20828 and a previously reviewed NDA (number 20628) provides an understanding of the pharmacokinetics of saquinavir administered as soft gelatin capsules and fulfills the requirements of Section 320 of the Code of Federal Regulations (21 CFR). Adequate pharmacokinetic information has been provided to support approval of FORTOVASE®. However, the Applicant should be highly encouraged to investigate the items listed in the Phase IV commitments.

LABEL

A label is attached to this review.

PHASE IV COMMITMENTS

The following Phase IV commitments can be obtained from the Applicant.

Prabhu Rajagopalan, Ph. D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence:

Janice B. Jenkins, Ph. D.
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

cc:	HFD-530	/NDA 20828
		/MO/Nguyen
		/CO/Struble
		/CSO/Kelly
	HFD-880	/Rajagopalan
	HFD-880	/TL/Jenkins
✓	HFD-880	/DPE III
✓	CDR	/Barbara Murphy

mw: c:\20828\ndafinal.doc, 10-31-97

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Reviewer : Prabhu Rajagopalan, Ph. D.

NDA : 20-828
TYPE : Final study report
DRUG : Saquinavir HGC
SPONSOR: Hoffmann-La Roche

SUBMISSION DATE : 08-27-97
DATE RECEIVED : 09-02-97
DRAFT REVIEW : 09-30-97
FINAL REVIEW : 10-01-97

Investigator and Study Location:

TITLE: The effect of rifabutin on the pharmacokinetics of saquinavir in HIV positive patients (Protocol number: WK 14841).

RATIONALE: Metabolism of saquinavir is mediated by cytochrome isozyme P450 3A. A drug interaction study with rifampicin, an inducer of CYP 3A4, resulted in 80% lower steady-state saquinavir plasma concentrations. Rifabutin, like rifampicin, is also an inducer of hepatic enzymes. This study was conducted to assess the drug interaction effects of saquinavir (in hard gelatin capsules (HGC)) and rifabutin.

OBJECTIVE: To compare the steady-state pharmacokinetics of saquinavir when dosed alone and in combination with rifabutin.

SUBJECTS: 13 HIV infected patients (mean age : 36.5 years; mean weight : 69.2 kg; 13/13 Caucasian and 13/13 males) participated in this study.

STUDY DESIGN: This was an open label study. The three treatments were:

Period I: Saquinavir HGC 600 mg t.i.d. for 7 days
Period II: Saquinavir HGC 600 mg t.i.d. + rifabutin 300 mg q.d. for 7 days.
Period III: Saquinavir HGC 600 mg t.i.d. + rifabutin 300 mg q.d. for 7 days.

There was no washout period between the three periods. On the last day of treatment in each period only one dose of saquinavir was administered. Saquinavir was administered within 10 minutes after completion of a meal and rifabutin was taken before breakfast. 1 patient was terminated from the study due to non-compliance. Some patients received azole antifungal agents for the treatment of adverse events. However, they did not receive these treatments at the time of pharmacokinetic assessments.

FORMULATIONS: Saquinavir hard gelatin capsules (200mg, batch number ROC215B) containing saquinavir in the form of saquinavir mesylate and rifabutin tablets (150 mg, Pharmacia batch number R4006) were used in this clinical trial.

SAMPLE COLLECTION:

Saquinavir: Blood samples were collected before dosing on Days 7, 14 and 21 and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours after saquinavir administration.

Rifabutin: Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours after saquinavir administration on Days 14 and 21.

Reviewer's note: From the flow chart of activities and the bioanalytical report it was noted that the first plasma sample for the analysis of rifabutin was obtained 2 hours after rifabutin administration. However, in the calculation of rifabutin pharmacokinetic parameters, the fact that plasma sample were collected relative to saquinavir dose has been ignored. This has resulted in errors in the calculation $AUC_{(0-24)}$. (See Pharmacokinetics section of this review).

ANALYTICAL METHODOLOGY:

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters were estimated by non-compartmental methods. $AUC_{(0-24)}$ was calculated by linear trapezoidal method. Transformed (*ln*) saquinavir $AUC_{(0-24)}$ and C_{max} were tested by ANOVA.

Saquinavir

The pharmacokinetic parameters of saquinavir are presented in Table 1 and the mean plasma concentration-time profiles are depicted in Figure 1. Following concomitant administration of saquinavir and rifabutin (Periods II and III), plasma concentrations of saquinavir were lower when compared to administration of saquinavir alone resulting in lower values for saquinavir AUC and C_{max}. However, t_{max} did not change due to concomitant administration.

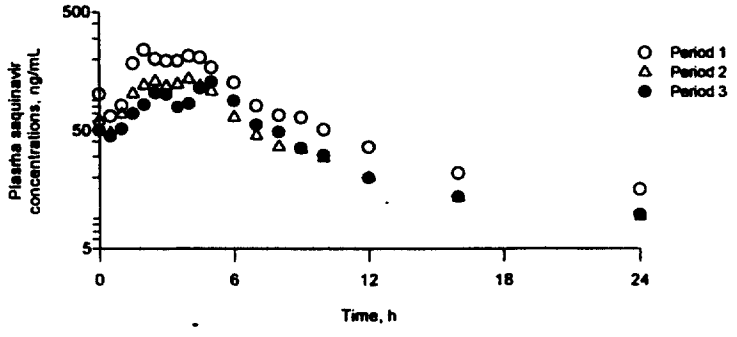


Figure 1

Table 1. Saquinavir pharmacokinetic parameters[1]

	Period I	Period II	Period III
AUC_{0-24}, ng.h/mL	1612 (57)	954.2 (47)	927.9 (63.1)
C_{max}, ng/mL	377 (107)	199 (44)	238 (75)
T_{max}, h	4	3.8	4.5
$T_{1/2}$, h	8.3	10.5	10.3

[1] Mean (%CV) for AUC and C_{max}, median for T_{max} and harmonic mean for $T_{1/2}$.

The results of statistical analysis of saquinavir pharmacokinetic parameters show statistically significant difference in Periods II and III with respect to Period I (Table 2). Individual values of saquinavir C_{max} and AUC_{0-24} in the three periods are shown in Figure 2.

Table 2. Saquinavir relative bioavailability.

Parameter	Period	Mean F_{rel}	95% CI
AUC_{0-24}, ng.h/mL	I		
	II	63	51 - 78
	III	57	47 - 71
C_{max}, ng/mL	I		
	II	69	41 - 115
	III	70	42 - 117

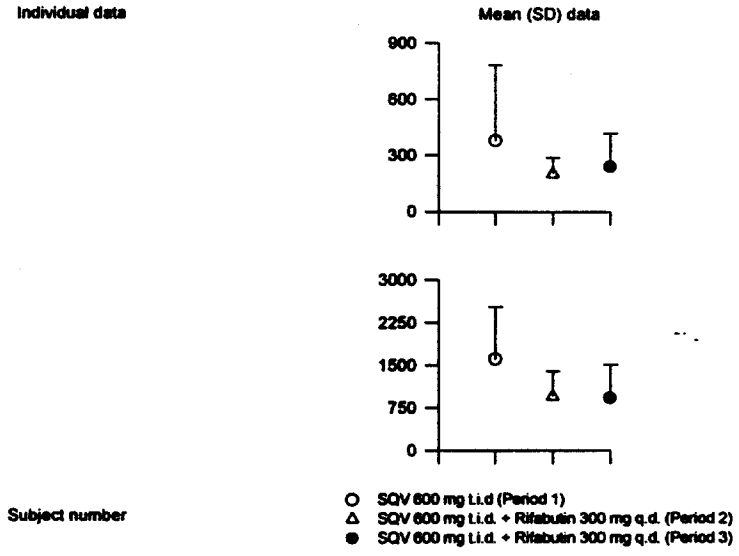


Figure 2

Rifabutin

The pharmacokinetic parameters of rifabutin are presented in Table 3 and the mean plasma rifabutin concentration-time profiles are depicted in Figure 3. The individual C_{max} and AUC values and the mean and standard deviation for rifabutin are depicted in Figure 4. Following concomitant administration of rifabutin and saquinavir (Period III), rifabutin plasma concentrations were slightly higher when compared to concentrations seen in Period II.

Reviewer's note: The inset in Figure 3 depicts mean plasma concentration-time profiles as reported by the Sponsor. However, for reasons mentioned in the Sample Collection section, the profiles in the inset are incorrect. From Figure 3 one can observe that the Sponsor has omitted the area under the curve from 0 to 2 hours in the calculation on AUC_{0-24}. Estimations by this Reviewer indicate that this omission results in a 5 to 15% error in the calculation of AUC_{0-24}. Since this error occurred in the calculation of AUC_{0-24} in both Period II and III, the AUC values reported by the Sponsor may be used in the comparison of rifabutin exposure in these periods. However, the T_{max} values reported the Sponsor are clearly not-acceptable.

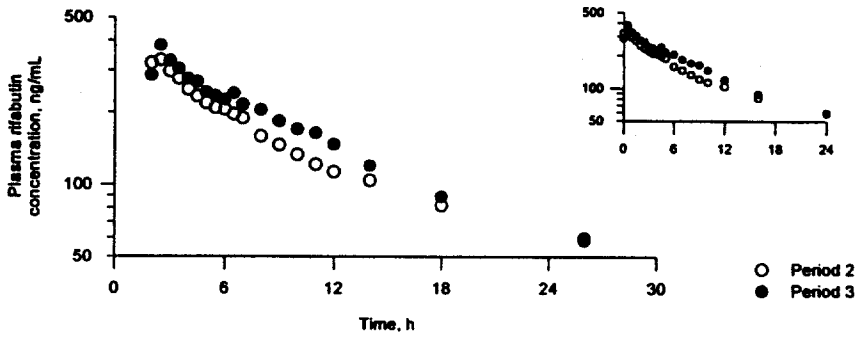


Figure 3

Table 3. Rifabutin pharmacokinetic parameters[1]

	Period II	Period III
AUC_{0-24}, ng.h/mL	3183 (45)	3547 (30)
C_{max}, ng/mL	384 (50)	413 (31)
T_{max}, h	0.33	0.92
$T_{1/2}$, h	12.17	11.60

[1] Mean (%CV) for AUC and C_{max}, median for T_{max} and harmonic mean for $T_{1/2}$.

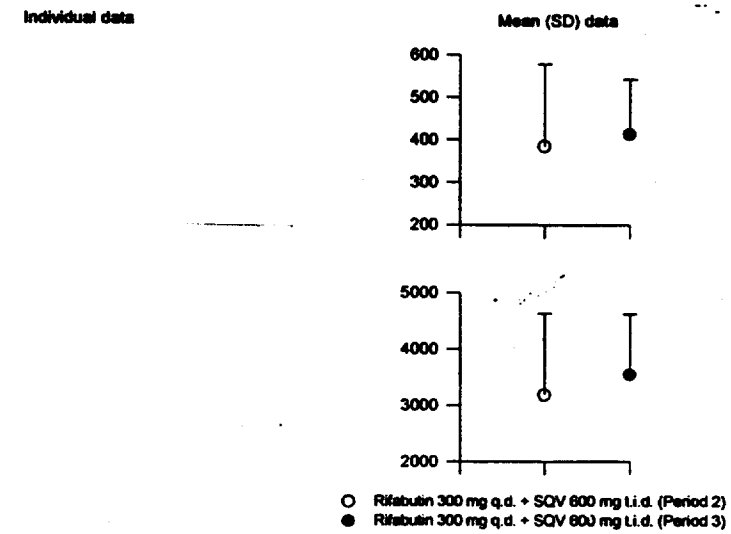


Figure 4

ADVERSE EVENTS: There were two severe adverse events. Patient 6 suffered a seizure on Day 18 of the study. This was considered possibly related to treatment. Laboratory safety tests and CT scan did not reveal any abnormality. Patient 10 reported periumbilical pain which lasted 11 days from Day 12.

Reviewer's note : In these two patients, plasma saquinavir and rifabutin levels were in the range of average values. A correlation between plasma drug levels and these adverse events was not apparent.

DISCUSSION AND CONCLUSIONS: This study was conducted to assess the drug interaction effects between saquinavir and rifabutin. Since subjects received multiple doses of both the drugs, clinically relevant information was obtained from this study. Since rifabutin pharmacokinetics following administration of rifabutin alone was not evaluated in these subjects, the Sponsor has made comparisons with historical values.

Saquinavir exposure during Period II was lower (approximately 40%) following administration of saquinavir and rifabutin. No further significant reduction was seen in Period III suggesting that maximum reduction in saquinavir exposure due to induction of hepatic enzymes had occurred during Period II. Mean plasma saquinavir concentration-time profile shows secondary peaks. The Sponsor notes that such secondary peaks were observed in 50% of the C_p-t profiles in all the three periods. Based on AUC, the relative bioavailability of saquinavir in Periods II and III was 63% and 57%, respectively.

Rifabutin plasma levels in Period II and III were similar indicating that maximum induction of hepatic enzymes had occurred within 7 days of rifabutin treatment. The Sponsor states that plasma rifabutin concentrations seen in this study are comparable to those reported in the literature (*Clinical Pharmacokinetics*. 28: 115-125). The label for both saquinavir HGC and SGC state that physicians should consider using an alternative to rifabutin when a patient is taking saquinavir.

COMMENTS TO THE SPONSOR:

1) According to the flow chart for pharmacokinetic profiles and plasma sample collection schedule, collection of plasma samples for the determination of rifabutin concentrations began around 2 hours after administration of rifabutin (and 0.5 hours after administration of saquinavir). It appears that you have not taken this into consideration in the calculation of pharmacokinetic parameters and, therefore, your estimations of rifabutin AUC_{0-24} and T_{max} are incorrect.

Comment conveyed to sponsor via a phone call 10-16-97.
E Kelly, CSO

R. Prabhu 10/01/97
Prabhu Rajagopalan, Ph. D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence: Janice Barnett Jenkins 10/6/97
Janice B. Jenkins, Ph. D.
Team Leader, Antiviral Drug Products Section

Statistical Report: Saquinavir Soft Gelatin Capsules, Human Pharmacokinetics and Bioavailability, Hoffmann-La Roche. Protocol WP15191.

OCPB reviewer: Prabhu Rajagopalan

Overview of Study

The objectives of this study were to show the bioequivalency of 2 formulations, a to-be-market version and a clinical trial version, with the formulation used in the Phase I and II clinical trials. This study was an open labeled, three period, six sequence, 3 treatment study in 30 healthy volunteers, 18 males and 12 females. Due to a high expected intrasubject variability, the protocol called for the primary determination of bioequivalency to be based on a ratio of the treatment AUC (unlabeled) and the AUC of a "stable isotope" administered with each treatment (labeled), $RAUC_A = AUC_A/AUCL_A$. This method of using a stable isotope design to help reduce the unexplained intrasubject variability has been used in several bioequivalence studies of saquinavir. As an exploratory secondary analysis, the sponsor also analyzed the ratio of Cmax of the unlabeled to the labeled dose, RCmax, as well as, the unlabeled Cmax and AUC.
The sponsor proposed to determine bioequivalence based on AUC alone and only consider the bioequivalence test of Cmax in an exploratory sense. Furthermore, the sponsor proposed to widen the Cmax bioequivalence region from 80-125% to 70-143%.

Problem

This method is used to increase the chances of passing bioequivalence in the presence of large variability instead of having to increase the sample size. However, in this study the variables RAUC and RCmax had larger CVs than the unlabeled Cmax and AUC [AUC 39% vs 35%, Cmax 51% vs 41%]. Subsequently one of the two formulations did not pass the bioequivalence criterion for RAUC, though the test of unlabeled AUC from the exploratory analysis did pass. The applicant now proposes to base bioequivalence on the unlabeled AUC, in which case, both formulation would pass for AUC.

Study design

This study is a three treatment, three period, six sequence design with 30 healthy volunteers, 18 Male and 12 Female. There were no dropouts or missing values.

Treatments:

A = /A22-00 - Current Phase I/II clinical trial formulation, (Reference)
B = /A31-00 - Phase I/II scaled-up clinical trial formulation,
C = /A25-00 - Proposed alternative market formulation,

Experimental Design:

Three Periods, Six Sequences
All possible sequences with 5 subject per sequence.

Endpoints analyzed for each of the 3 treatments:

AUCun	area under plasma concentration time curve for the unlabeled dose.
AUClab	area under plasma concentration time curve for the labeled dose.
RAUC	ratio of AUCun to AUClab.
Cmaxun	maximum concentration of the unlabeled dose.
Cmaxlab	maximum concentration of the labeled dose.
RCmax	ratio of Cmaxun to Cmaxlab.

The Model

For a given endpoint, we used the following statistical model. y_{ij} is the log transformed endpoint for subject i at period j.

$$y_{ij}=\beta_0+\beta_1 T_{1ij}+\beta_2 T_{2ij}+\beta_3 Seq_{1ij}+\beta_4 Seq_{2ij}+\beta_5 Seq_{3ij}+\beta_6 Seq_{4ij}+\beta_7 Seq_{5ij}+\beta_8 Per_{1ij}+\beta_9 Per_{2ij}+b_i+e_{ij}$$

with $b_i \sim N(0, d^2)$ and $e_{ij} \sim N(0,\sigma^2)$.

T_{Xij} = 1 if treatment X, = 0 otherwise
Seq_{Xij} = 1 if in sequence X, = 0 otherwise
P_{Xij} = 1 if period X, = 0 otherwise

The fixed effects are (β_0, β_1, β_2, β_3, β_4, β_5, β_6, β_7, β_8, β_9). The random effect for subject i is b_i. e_{ij} is an independent random error term. The applicant did not include a sequence effect but instead included a carryover effect. Neither of these variables changed the results.

SAS Code:

```
proc mixed;
class seq subj per trt;
model endpoint = seq per trt /solution;
random int / subject=subj solution g;
lsmeans trt/cl pdiff alpha=.1;
run;
```

Covariance Structure:

The covariance structure specified by this model for individual i's log transformed endpoints $y_i = [y_{i1}, y_{i2}, y_{i3}]^T$ is as follows:

$$var(y_i) = Zd^2Z' + R = \begin{bmatrix}1\\1\\1\end{bmatrix} d^2 \begin{bmatrix}1\\1\\1\end{bmatrix}' + \sigma^2 \begin{bmatrix}1&0&0\\0&1&0\\0&0&1\end{bmatrix} = \begin{bmatrix}d^2+\sigma^2 & d^2 & d^2\\ d^2 & d^2+\sigma^2 & d^2\\ d^2 & d^2 & d^2+\sigma^2\end{bmatrix}$$

This covariance structure allows for a correlation within subject over the three periods, where the

covariance between values from two periods on one subject is d^2. The variability of each measurement is the sum of the between subject error (d^2) and the within subject error (σ^2). The independent random error associated with each measurement is contained in the "simple" diagonal R matrix. Zd^2Z' is the matrix that induces the correlation among the responses within a subject. Since different subjects are assumed independent, the overall covariance structure is block-diagonal with subject blocks.

The Data

The data is shown in Figures 1 (Cmax) and 2 (AUC). The applicant stated 3 key assumptions needed for this technique of using a labeled dose to be valid. The first is that the labeled formulation should, on average, give the same result within each treatment arm. The middle panel in each of the figures shows the AUC or Cmax for the labeled dose for each treatment. Visual inspection does not show large differences between the three treatments. The second assumption is that there should be a high degree of correlation between the parameters from the labeled and unlabeled formulations. The overall correlation between labeled and unlabeled formulations for Cmax is approximately 0.57 and for AUC is 0.71. Table 1 lists the correlations for each treatment. The third assumption is that the labeled and unlabeled formulations should not interact differently for different treatments.

Table 1.

Correlation of labeled to unlabeled	AUC	Cmax
Treatment A	0.750	0.396
Treatment B	0.687	0.765
Treatment C	0.707	0.606

Results of Bioequivalence Analysis

Our analysis of bioequivalence do not differ from the sponsor's. Table 2 lists the results from Table 7 of Roche's final study report (p.26). Based on the bioequivalence test as defined in the protocol, treatment C would be considered bioequivalent to A, though B would not. Based on the 1992 FDA Guidance *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design* bioequivalence of the compounds is concluded if all of the confidence intervals for the ratios (T/R) of each of the endpoints for the parent compound and the metabolites of interest lie entirely in the interval (0.8, 1.25). Under this criterion, neither formulation would pass, since RCmax fails for both formulations. If the amendment of the protocol by Roche for a range of 70 - 143% were allowed then treatment B would be equivalent for RCmax.

Table 2:

Parameter	Treatment	Estimate	Estimate and 90% C.I.	Conclusion
RAUC	A	5.13	100 (Reference)	
	B	5.98	117 [99,137]	No equivalence
	C	5.42	106 [90,124]	Equivalence
RCmax	A	4.93	100 (Reference)	
	B	5.65	115 [93,141]	Equivalence, based on region of [70-143%]
	C	5.74	117 [95,144]	No equivalence

As stated in the protocol, analyses on unlabeled AUC and CMAX would also be performed though as an exploratory analysis only. In this analysis both B and C were found to be bioequivalent to A for both AUC and CMAX, if the wider interval for Cmax wās allowed. The results of the sponsor's analysis, from Table 8 (p.26) of the final study report, are given in Table 3.

Table 3:

Parameter	Treatment	Estimate	Estimate and 90% CI	Conclusion
Unlabeled AUC 0-12	A	1568	100 (Reference)	
	B	1575	100 [87,116]	Equivalence
	C	1572	100 [87,116]	Equivalence
Unlabeled Cmax	A	604.0	100 (Reference)	
	B	612.2	101 [86,120]	Equivalence
	C	667.1	110 [93,131]	Equivalence, based on region of [70-143%]

Roche also performed bioequivalence tests on the labeled dose. Since this is the same drug/formulation, we would assume that it would pass bioequivalency for both Cmax and AUC. From Roche's analysis treatment B did not pass bioequivalence for AUC for the labeled dose, 86%, CI [73%, 102%] or Cmax, 88%, CI [74%,105%]. This could help explain why RAUC failed for treatment B.

Conclusion

The question here is: are these two treatments (B and C) equivalent to the phase I and II trial formulation (A)? Should the results from the exploratory analysis serve as the primary analysis? There is a general statistical problem with changing proposed analyses technique after finding a negative result. Performing multiple tests cause an increase in the type I error rate (the probably

of concluding bioequivalence given they are not equivalent). Also, the sponsor is arguing that the proposed test in no longer valid. Though if the results were positive, the proposed technique most likely would not have been questioned. This would then give the sponsor two chances for concluding bioequivalence.

A second problem with changing the method is that the sponsor states that there were biological reasons for the failure. As stated in Roche's Final Study Report (p.33), at least 8 out of a total of 90 observations had very high ratios of AUCs which were associated with "markedly different concentration vs time profiles for labelled and unlabelled saquinavir during the absorption phase." The sponsor shows two graphs to illustrate how a concentration time curve for one of these 8 observations differs from a typical observation (Figures 4 and 4a of Roche's Final Study Report, p.34). These figures were recreated in Figure 3 below. The top panel, subject 21, represents a typical concentration time profile (RAUC=4.68). The bottom panel, subject 11, shows a concentration time profile with an uncharacteristically large relative parameter for AUC (RAUC=23.14). It seems clear from these figures that the AUC unlabeled can be greatly affected by the administration of the labeled dose. Since the labeled dose will not be administered with the unlabeled dose in practice, the values of AUC and Cmax unlabeled for these subjects with altered concentration time profiles will not be consistent with what would be seen in a clinical setting. A bioequivalence test on these parameters would not be valid.

Karen M. Higgins

Karen M. Higgins, Sc.D.
Staff Fellow, QMR
August 11, 1997

Donald J. Schuirmann

Concur: Donald J. Schuirmann
Acting Director, QMR
August 11, 1997

cc:
Original NDA 20-828
HFD-705 QMR Chron
HFD-880 Prabhu Rajagopalan
HFD-705 Karen Higgins
HFD-705 Donald Schuirmann
HFD-880 Janice Jenkins
HFD-880 John Lazor
HFD-530 Kelly

Figure 1

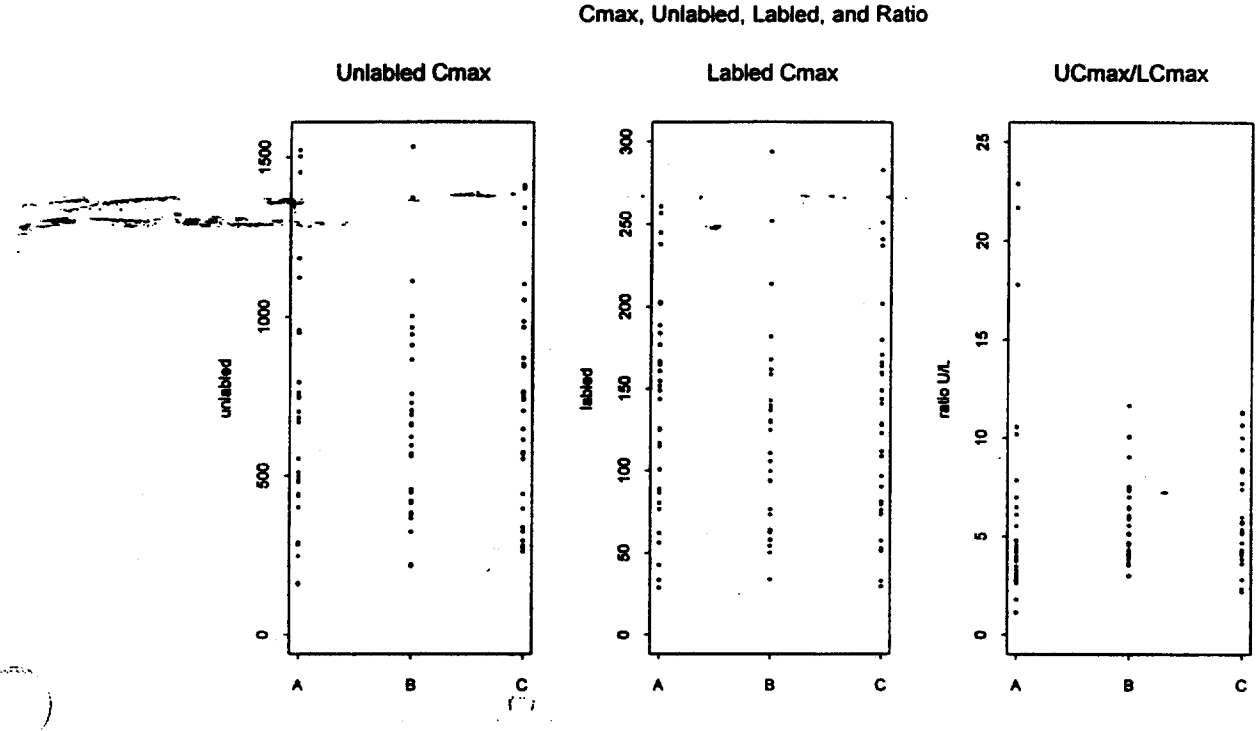


Figure 2

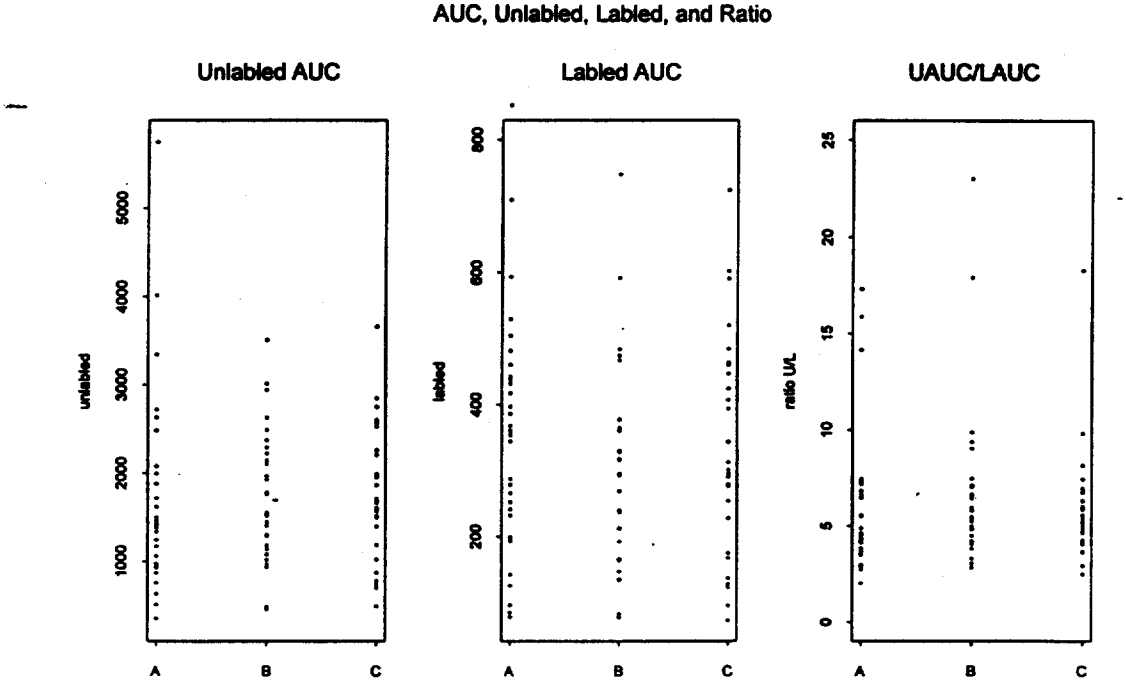
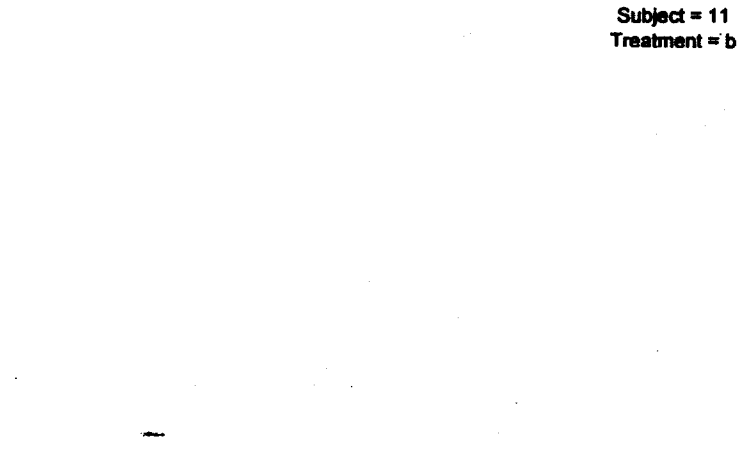


Figure 3



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20828

ADMINISTRATIVE DOCUMENTS

Interoffice Memo

Roche Hoffmann-La Roche
A Member of the Roche Group

To: Lynn Hill

Date: January 16, 1997

From: Alan P. Kass APK

Dept.: Patent Law Department

Subject: **Patent Information for Saquinavir Formulation NDA**

Attached are patent information and market exclusivity request documents, together with literature search, for the above NDA. An electronic version of the patent information and market exclusivity request documents will be sent to you in electronic form.

The clinical investigator should review the market exclusivity request and the literature search and then complete the market exclusivity request.

The patent application directed to the new saquinavir formulation is pending before the United States Patent and Trademark Office. Should a patent to the new formulation issue prior to approval of the NDA, we will send you a revised patent information document. Additionally, please keep us advised as to the review and approval of the NDA before the FDA so that we can review and determine if an application for patent term extension is appropriate.

/APK
Attachments
cc (w/o attachs.): Ms. Robin Conrad
Mr. George Johnston
Dr. Clive Spiegler
35580

Pending NDA 20-828
[Invirase™ (saquinavir) capsule]
Patent Information/Market Exclusivity Request

Pursuant to Section 505 of the Federal Food, Drug & Cosmetic Act, the following information is submitted for inclusion in the above-noted NDA:

1. Patent Information
2. Market Exclusivity Information

Confidential Submission

Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 U.S.C. 552). It is requested that this submission not be published until the New Drug Application has been approved.

PATENT INFORMATION

1. Active Ingredient(s): Saquinavir

2. Strength(s): 200 mg capsules

3. Trade Name: INVIRASE™

4. Dosage Form and Route of Administration: Capsules, Oral

5. Applicant (Firm) Name: Hoffmann-La Roche Inc.

6. NDA Number: NDA 20-828

7. First Approval Date:

8. Exclusivity: First ANDA can not be submitted until 3 years after date of NDA approval.

9. Patent Information: 5,196,438
Nov. 19, 2010**
Drug Substance
Hoffmann-La Roche Inc.

While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy or completeness of the information contained therein.

CONFIDENTIAL INFORMATION

**This date does not include any extension under 35 U.S.C. 156.

EXCLUSIVITY SUMMARY for NDA # 20-828 SUPPL # _____

Trade Name FORTOVASE™ **Generic Name** Saquinavir Soft Gelatin Capsule

Applicant Name Hoffmann-LaRoche, Inc. **HFD-**530

Approval Date November 7, 1997

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) ____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95

cc: Original NDA 20828
Division File 20828
HFD-85/ Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /_X_/ NO /___/

If yes, NDA # 20-628 Drug Name INVIRASE®

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ___ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # ___ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain: _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

_____ _____

Signature Date

Title:_____

_____ 11-7-97

Signature of Division Director Date

(Acting)

cc: Original NDA
Division File
HFD-85/Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-828 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-530 Trade and generic names/dosage form: FORTOVASE™ (Saquinavir Soft Gelatin Capsule Action: AP AE NA

Applicant Hoffmann-La Roche, Inc. Therapeutic Class _____

Indication(s) previously approved None
Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

X a. **A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.**

__ b. **A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.**

X c. **The applicant has committed to doing such studies as will be required.**

- X (1) Studies are ongoing.
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply, attach an explanation, as necessary.**

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Christine Kelly 11-7-97

Signature of Preparer and Title / Date

cc: Orig NDA/PLA/PMA # N20-828
HFD 530 /Div File 20-828
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 11/6/97)

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 335a (a) and (b), in connection with this application.