CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-785

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21785	Submission Date(s): 18June2004
Brand Name	INVIRASE® FILM-COATED 500-mg Tablets
Generic Name	Saquinavir Mesylate
Reviewer	Jennifer L. DiGiacinto, Pharm.D.
Team Leader	Kellie Reynolds, Pharm.D.
OCPB Division	DPE III
OND Division	DAVDP
Applicant	Hoffman La Roche
Relevant IND(s)	IND 41099
Submission Type; Code	Priority (1P)
Formulation; Strength(s)	Saquinavir Mesylate 500-mg Tablet
Indication	Treatment of HIV infection in combination with other antiretroviral drugs

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1. EXECUTIVE SUMMARY

Saquinavir mesylate (SQV) is a protease inhibitor (PI), which is currently approved as a capsule formulation (INVIRASE® Hard Gel Capsules 200-mg (SQV HGC)) for the treatment of HIV infection in adults at least 18 years of age when it's co-administered with low dose ritonavir (RTV). The approved dosing regimen is SQV 1000-mg/RTV 100-mg BID. The applicant has developed a new SQV film-coated tablet (FCT) formulation (500-mg) that will significantly decrease the daily SQV pill burden of this regimen (4 tablets vs. 10 capsules). In support of this NDA, the Applicant addressed the following issues:

- The SQV FCT has similar relative bioavailability (BA) to the currently marketed SQV HGC when combined with low dose RTV and administered under fed conditions.
- The SQV FCT is not bioequivalent (BE) to the SQV HGC when administered alone under fed conditions. Because SQV FCT will always be administered with RTV, BE to the SQV HGC is not critical.

1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant is acceptable. There are no major clinical pharmacology and biopharmaceutics issues related to this submission.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

SQV FCT will be administered in combination with low dose RTV as part of an antiretroviral regimen. The low dose RTV is used as a pharmacokinetic (PK) enhancer to the SQV concentrations. The SQV + RTV (1000-mg/100-mg BID) regimen was approved by the Agency on December 24, 2003. This NDA contains a pivotal relative BA study (BP17359), a pivotal BE study (BP17653), and dissolution data for the new SQV FCT formulation.

BP17359 is the pivotal relative BA study that compares the new SQV FCT + RTV to SQV HGC + RTV under fed conditions. This was a multi-center (2 centers), open-label, randomized, two-sequence, four-period, two-treatment, replicated, crossover study conducted in 100 healthy adult subjects (93 males and 7 females). The results of this pivotal relative BA study demonstrated that the SQV FCT formulation achieves similar BA as the current marketed SQV HGC formulation when both formulations are administered with low dose RTV under fed conditions. See Table 1 below.

Table 1. Mean Exposures and Mean Exposure Ratios (90% Confidence Interval) for SQV (N= (7 females + 87 males) x 4 PK Profiles)

PK Parameter	Treatment	Mean Exposure	Mean % Ratio	90% CI
$AUC_{0\text{-}inf}$ (ng·h/mL):	SQV HGC/RTV SQV FCT/RTV	28420 31223	109.86	[104.41, 115.59]
C_{max} (ng/mL)	SQV HGC/RTV SQV FCT/RTV	3295 3924	119.07	[113.67, 124.72]

A gender effect with SQV PK was noted in BP17359, with the female subjects achieving higher SQV exposures (AUC ↑56% and C_{max} ↑26%) compared to the male subjects. Unfortunately, the small number of female subjects in BP17359 (N=7 females and N=93 males) makes the interpretation difficult. No increase in adverse events (ADEs) was seen in females as compared to males enrolled in the study. The gender effect seen in BP17359 has been reported in other SQV studies in the literature (MaxCmin, ACTG-359 and BP17653) and it's hypothesized to be related to the differing amounts of CYP3A4 enzyme and p-glycoprotein (PGP) in females compared to males. Due to the large variability seen in SQV concentrations (both genders), interpreting the clinical significance of the safety and efficacy data relative to gender effect is difficult.

BP17653 is the pivotal BE study that compares the new SQV FCT to the currently marketed SQV HGC when administered alone and under fed conditions. This was a single-center, open-label, randomized, two-sequence, four-period, two-treatment, replicated, crossover study conducted in 20 healthy adult subjects (10 males and 10 females). In accordance with the FDA Bioavailability (BA) and BE Studies for Orally Administered Drug Products Guidance, BE with respect to formulation is concluded if the 90% CI for the ratio (test to reference) falls within 80% to 125% for C_{max} and AUC_{0-t} and AUC_{0-inf}. SQV FTC (test product) did not meet the BE criteria when compared to the current marketed SQV HGC formulation (reference product). See table 2 below.

Table 2. Mean Exposures and Mean Exposure Ratios (90% Confidence Interval) for SQV [N= (10 Females + 10 Males) x 4 PK Profiles]

PK Parameter	Treatment	Mean Exposure[a]	Mean Exposure Ratio	90% CI
AUC_{0-inf} (ng·h/mL)[b]:	**Females:**			
	SQV HGC	1086		
	SQV FCT	1485	1.37	[1.17, 1.59]
	Males:			
	SQV HGC	1039		
	SQV FCT	1028	0.99	[0.85, 1.15]
C_{max} (ng/mL)	**Females:**			
	SQV HGC	306		
	SQV FCT	395	1.29	[1.03, 1.62]
	Males:			
	SQV HGC	265		
	SQV FCT	278	1.05	[0.84, 1.31]
	All:			
	SQV HGC	285		
	SQV FCT	332	1.16	[0.99, 1.37]

a: exponential least square means of ln-transformed exposure parameters
b: overall estimation of mean exposures and exposure ratios for the two treatments not provided due to the finding of a gender by treatment interaction
Data Source: Applicant's Module 5, Volume 12 page 11

The AUC_{0-inf} and C_{max} values achieved by both SQV formulations in this study were approximately 20 to 25-fold less and 10 to 15-fold less compared to the AUC_{0-inf} and C_{max} values reported in the pivotal relative BA (Study BP17359) when SQV was administered with low dose RTV. The inter-subject variability values were much higher in this study when compared to the values reported in BP17359 (AUC 49% to 79% compared to 45% to 50% and C_{max} 58% to 79% compared to 38% to 42%).

There was evidence of a difference in the relative performance of the two SQV formulations between male and female healthy volunteers with respect to the $AUC_{0\text{-}inf}$ of SQV. For female subjects, a mean exposure ratio of SQV FCT vs. SQV HGC for $AUC_{0\text{-}inf}$ was 1.37 [90% CI: 1.17, 1.59] and for male subjects 0.99 [90% CI: 0.85, 1.15]. Because of this gender by treatment finding for $AUC_{0\text{-}inf}$ values, an overall (both male and female study subjects) the mean exposures and exposure ratios for the two treatments was not conducted by the applicant. The C_{max} values reported did not indicate such a difference in the relative performance of the two formulations between genders even though females in general achieved higher C_{max} values compared to the male study subjects. These findings are not considered clinically significant because SQV FCT will not be administered alone as a sole PI. In addition, this formulation performance difference was not duplicated in BP17359 where SQV FCT was administered with low dose RTV; the intended way SQV FCT will be administered upon its approval.

The dissolution of SQV FCT is assessed using USP Apparatus with ——— operated ———. The dissolution medium is ——— at pH — and maintained at 37.5° C. The amount of SQV FCT dissolved is determined by UV detection at ——— cell. The single time-point specification of — dissolved at ——— is proposed for the SQV FCT tablets (Q=— dissolved in ———). The proposed dissolution method and specification for INVIRASE® Film-Coated 500-mg Tablet is acceptable.

2. QUESTION BASED REVIEW

2.1 General Attributes of the Drug
Not applicable.

2.2 General Clinical Pharmacology
Not applicable.

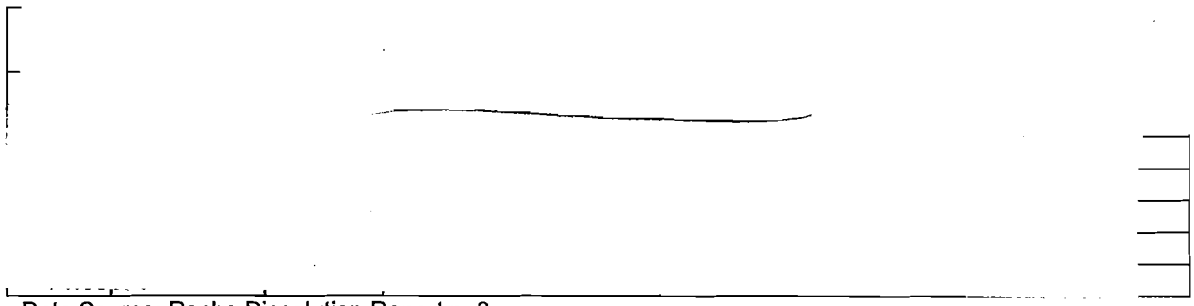
2.3 Intrinsic Factors
Not applicable.

2.4 Extrinsic Factors
Not applicable.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

SQV is a BCS class 4 drug product with low solubility and a low permeability. A drug substance is classified as highly soluble when the highest dose strength is soluble in ≤ 250 mL of aqueous media over the pH range of 1.0 -8.0. SQV is a weak acid with a dissociation constant of (pKa) of 7.0. The solubility of SQV depends strongly on the pH of the test medium. See Table 3 below.



Data Source: Roche Dissolution Report p. 3

SQV is a low permeability drug because the oral absorption is estimated to be low (approximately 20-30%).

2.5.2 What is the in vivo relationship of the proposed SQV FCT formulation to the SQV HGC currently marketed formulations in terms of comparative exposure?

BP17359 (relative BA study) compares the new SQV FCT + RTV to SQV HGC + RTV administered under fed conditions. The new SQV FCT formulation achieves similar BA as the current marketed formulation SQV HGC when both SQV formulations are administered with low dose RTV under fed conditions. Once approved, SQV FCT will only be administered in combination with low dose RTV as part of an antiretroviral regimen. See Table 4.

BP17653 (pivotal BE study) compares the new SQV FCT to SQV HGC administered alone under fed conditions. The SQV FCT (INVIRASE® FILM-COATED 500-MG Tablet) is not BE to the current marketed SQV HGC (INVIRASE® Capsule). These findings are not considered clinically significant because SQV FCT will not be administered alone as a sole PI. See Table 5.

A gender effect with SQV PK was noted in both BP17359 and BP17653 with the female subjects achieving higher SQV exposures. No increase in adverse events (ADEs) reporting was seen in females as compared to males enrolled in the two separate studies. The gender effect has been reported in other SQV studies in the literature (MaxCmin and ACTG-359) and it's hypothesized to be related to the differing amounts of CYP3A4 enzyme and p-glycoprotein (PGP) in females compared to males. For further discussion on the gender effect, please see the individual study reviews in the Appendix.

The geometric least square means (GLS) and 90% CI values for SQV FCT and SQV HGC are listed in the Table 4 below.

Table 4. Mean Exposures and Mean Exposure Ratios (90% Confidence Interval) for SQV (N= (7 females + 87 males) x 4 PK Profiles) (BP17359 Relative BA Study)

PK Parameter	Treatment	Estimated Mean Exposure	Estimated Mean %	90% CI
$AUC_{0\text{-}inf}$ (ng·h/mL):	SQV HGC/RTV	28420	100.00	
	SQV FCT/RTV	31223	109.86	[104.41, 115.59]
C_{max} (ng/mL)	SQV HGC/RTV	3295	100.00	
	SQV FCT/RTV	3924	119.07	[113.67, 124.72]

The geometric least square means (GLS) and 90% CI values for SQV FCT and SQV HGC are listed in the Table 5 below.

Table 5. Mean Exposures and Mean Exposure Ratios (90% Confidence Interval) for SQV [N= (10 Females + 10 Males) x 4 PK Profiles] (BP17653 BE Study)

PK Parameter	Treatment	Mean Exposure[a]	Mean Exposure Ratio	90% CI
$AUC_{0\text{-}inf}$ (ng·h/mL)[b]:	**Females:**			
	SQV HGC	1086		
	SQV FCT	1485	1.37	[1.17, 1.59]
	Males:			
	SQV HGC	1039		
	SQV FCT	1028	0.99	[0.85, 1.15]
C_{max} (ng/mL)	**Females:**			
	SQV HGC	306		
	SQV FCT	395	1.29	[1.03, 1.62]
	Males:			
	SQV HGC	265		
	SQV FCT	278	1.05	[0.84, 1.31]
	All:			
	SQV HGC	285		
	SQV FCT	332	1.16	[0.99, 1.37]

a: exponential least square means of ln-transformed exposure parameters
b: overall estimation of mean exposures and exposure ratios for the two treatments not provided due to the finding of a gender by treatment interaction
Data Source: Applicant's Module 5, Volume 12 page 11

The clinical formulation (SQV FCT used in the pivotal BE study BP17653) and the proposed commercial formulation have the same tablet kernel formulation. Slight modifications to the film-coating were employed in the clinical batches in order to simplify the coating process and to utilize a commercially available film-coating system.

2.5.3 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

There was no food effect study conducted since the current SQV labels recommend SQV (INVIRASE® and FORTOVASE®) to be taken with food. All BE and relative BA studies were conducted under fed conditions. SQV mesylate (INVIRASE®), when administered alone, has poor BA regardless if it's a capsule or tablet formulation (approximately 4-18%). Administration with food improves SQV BA. SQV mesylate will

always be taken with low dose RTV under fed conditions, to achieve therapeutic concentrations.

2.5.4 *How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

The proposed dissolution method is the currently approved dissolution method for Invirase® 200-mg Capsules, with the exception of an analysis wavelength of 300 nm instead of [redacted]. The UV method has been validated regarding selectivity, accuracy, linearity, and precision in the range of [redacted] of the working concentration [redacted] and has proved to be suitable for the determination of the dissolution rate of the SQV drug substance in Invirase® Film-Coated Tablets 500-mg. In addition, the dissolution method selection provides discriminatory power to detect manufacturing process variations (increased temperature and increased relative humidity).

Proposed Dissolution Method and Specification
The proposed dissolution method for INVIRASE® FILM-COATED 500-mg Tablet is as follows:

Apparatus USP [redacted]
Rotation Speed [redacted]
Temperature: 37.5° C ± 0.5° C
Medium: [redacted]
Sampling Time: [redacted] for whole profiles
Sample Amount: 6 x 1 film-coated tablet individually
Filter:
Analytical Method: [redacted]

The proposed dissolution specification for Invirase® is Q [redacted] dissolved in [redacted].

The proposed dissolution method and specification are acceptable.

2.6 Analytical Section
A validated [redacted] HPLC with tandem mass spectrometric detection analytical method was used to determine SQV concentrations in plasma. This assay is acceptable. For further assay information, refer to the individual study reports in the Appendix.

3. LABELING RECOMMENDATIONS

CLINICAL PHARMACOLOGY

The following tablet information has been added the INVIRASE® Capsule-Tablet label.

Pharmacokinetics
Similar bioavailability was demonstrated when INIVIRASE 500 mg FCT (2x 500 mg) and INVIRASE 200 mg capsule (5 x 200 mg) were administered with low dose ritonavir (100 mg) under fed conditions. The ratio of mean exposures (90% confidence intervals) of tablets vs. capsules were 1.10 (1.04-1.16) for AUC0-∞ and 1.19 (1.14-1.25) for C_{max}.

Gender, Race, and Age
A gender difference was observed, with females showing higher saquinavir exposure than males (mean AUC increase of 56%, mean C_{max} increase of 26%), in the relative bioavailability study comparing INVIRASE 500 mg film coated tablets to the INVIRASE 200 mg capsules in combination with ritonavir. There was no evidence that age and body weight explained the gender difference in this study. A clinically significant difference in safety and efficacy between men and women has not been reported with the approved dosage regimen (saquinavir 1000-mg/ritonavir 100-mg bid).

HOW SUPPLIED
INVIRASE 500-mg film coated tablets are light orange to greyish- or brownish-orange, oval cylindrical, biconvex tablets with ROCHE and SQV 500 imprinted on the tablet face—bottles of 120 (NDC XXXX-XXXX-XX).

The capsules and tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] in tightly closed bottles.

7 Page(s) Withheld

0 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4.1.2 Pivotal Relative Bioavailability (BP17359)

Current dosing regimens of many protease inhibitors (PI) used for the treatment of HIV infection include their use in combination with low dose ritonavir (RTV) to enhance the pharmacokinetic (PK) exposures of the selected PI. Recently (December 2003), Roche received FDA approval for a new dosing regimen for saquinavir (SQV), which is their approved PI marketed as Invirase® Hard Gel Capsules (HGC) and Fortovase® Soft Gel Capsules (SGC). The new approved dosing regimen for SQV is 1000-mg SQV + 100-mg RTV BID. This new PK enhanced SQV regimen decreases the pill burden associated with taking SQV and decreases the number of SQV administrations per day (from TID to BID). The Applicant now submits an NDA for Invirase® Film-Coated Tablets 500-mg. The new tablet formulation will further decrease the pill burden for patients prescribed the SQV + RTV regimen from ten SQV capsules/day to four SQV tablets/day.

The new SQV film-coated tablet (FCT) formulation contains the same salt, saquinavir mesylate, as in Invirase®. Therefore, Invirase® was chosen as the reference product for establishing the relative bioavailability (BA) of the new FCT formulation to the current marketed formulation. A previous pilot BA study was conducted with 20 healthy male volunteers and the results showed the FCT formulation to have similar BA to the Invirase® capsule when co-administered with low dose RTV under fed conditions (BP17058). This pilot study provided the basis for the Applicant's design of BP17359, the pivotal relative BA study. This report summarizes the findings of BP17359.

Study Design

This was a multi-center (2 centers), open-label, randomized, two-sequence, four-period, two-treatment, replicated, crossover study conducted in a total of 100 healthy adult subjects under fed conditions. Male subjects were recruited at both sites and female subjects were recruited at one site. Each subject was randomized to one of two different sequences (ABAB or BABA). On PK days (Days 14, 17, 20, and 23), a standard high fat breakfast was administered prior to study drug administration. The table below provides a description of how study drugs were administered.

Table 1. Overview of Study Design

Screen	Day 1	Day 14	Day 17	Day 20	Day 23	Day 24	FU[d]
D -28 to D -1	Start RTV[a]	SD SQV[b]	SD SQV[b]	SD SQV[b]	SD SQV[b]	End RTV[c]	Day 39 to 45

SD = single dose
a: RTV administered BID (Q12H) (± 1), 24 days continuously
b: In the mornings of Days 14, 17, 20, and 23 RTV is administered with a single dose of SQV as per randomization. SQV was not administered on other days.
c: On Day 24, only the morning dose of RTV was administered
d: FU = follow up

Study Treatments

Treatment A (Reference Treatment): Invirase® HGC 1000-mg + RTV 100-mg
Treatment B (Test Treatment): Invirase® FCT 1000-mg + RTV 100-mg

Table 2. Study Medication

Drug	Strength	Dosage Form	Batch Number
Invirase® FCT	500-mg	Tablet	PT9511B34
Invirase® HGC	200-mg	Capsule	B1126
Norvir® (RTV) Capsules	100-mg	Capsule	02080VA

Meal Composition

Table 3. Standard High Fat Breakfast

Food	Quantity	Protein (grams)	Lipids (grams)	CHO (grams)
Whole Milk	227 mL	7.49	19.98	10.67
Eggs	2 eggs	12.5	11	2
Butter	15 grams	0.07	12.3	0
Gruyere Cheese	30 grams	8.82	8.64	0.06
Sandwich Loaf	2 slices	3.12	1.17	21.06
Hash Browns	2 pieces	3.6	10	32.4
Total (grams)		35.6	63.09	66.19
Calories (kcal)		142.4	567.81	264.76
Calories (%)		14.6	58.2	27.2

Total Calories: 975

Study Demographics

Table 4. Summary of Demographics

Sex:	
Male	93 (93%)
Female	7 (7%)
n	100
Race:	
Caucasian	95 (95%)
Black	2 (2%)
Oriental	-
Other	3 (3%)
n	100
Age:	
Mean	36.5 yr
SD	12.33
Weight:	
Mean	77.66 kg
SD	10.03
Height:	
Mean	175.6 cm
SD	7.13

Data Source: Applicant's Module 5, page 37

PK Sampling

Venous blood samples were collected to measure SQV concentrations at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours after SQV administration on Days 14, 17, 20, and 23.

PK Analysis

PK parameters were calculated using WinNonlin (Version 4.0.1) non-compartmental methods. The following PK parameters of SQV were calculated for each subject from the concentration time data obtained during the PK sampling: C_{max}, t_{max}, $t_{½}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and CL/F.

- All pharmacokinetic parameters for testing the relative BA were analyzed using analysis of variance (ANOVA).
- For the assessment of the formulation relative BA, a 90% CI was obtained for the geometric mean ratio (Treatment A as reference product and Treatment B as test product).
- Similar relative BA was concluded if the 90% CI intervals were within the 80-125% range for C_{max} and AUC.

BP17359 Assay Validation

Table 5. Synopsis of Bioanalytical Report

Protocol Number	BP17359
GLP	Yes
Sample Origin	BP17359 Study
Species	Human
Biological Material	Plasma
Analytical Method	[redacted] HPLC with tandem mass spectrometric detection
Sensitivity of Assay	
Precision (%CV)	
Accuracy	

Reviewer Comment: The assay is acceptable.

BP17359 Study Results

The summary statistics of SQV FCT and SQV HGC PK parameters are listed in the table below.

Table 6. PK Parameters [Mean (CV)] of SQV after Treatment with Invirase® (HGC/RTV) and Invirase® (FCT/RTV)

Parameter	Treatment A: HGC/RTV	Treatment B: FCT/RTV
Number of observations	188	188
$AUC_{0\text{-}inf}$ (ng·h/mL):		
Arithmetic Mean	27805 (51%)	29734 (45%)
Geometric Mean	24430	26826
C_{max} (ng/mL)		
Arithmetic Mean	3322 (39%)	3911 (36%)
Geometric Mean	3064	3644
t_{max} (h)		
Median	5	4
(min, max)	(2,14)	(2,8)
t½ (h)		
Arithmetic Mean	6.21 (25%)	6.43 (21%)
Geometric Mean	6.04	6.30
CL/F (mL/min)		
Arithmetic Mean	46999 (57%)	41814 (53%)
Geometric Mean	40932	37278

Data Source: Applicant's Module 5, page 39

The geometric least square means (GLS) and 90% CI values for SQV FCT and SQV HGC are listed in the table below.

Table 7. Estimated Mean Exposures and Mean Exposure Ratios (90% Confidence Interval) for SQV (N= (7 females + 87 males) x 4 PK Profiles)

PK Parameter	Treatment	Estimated Mean Exposure	Estimated Mean %	90% CI
$AUC_{0\text{-}inf}$ (ng·h/mL):	SQV HGC/RTV	28420	100.00	
	SQV FCT/RTV	31223	109.86	[104.41, 115.59]
C_{max} (ng/mL)	SQV HGC/RTV	3295	100.00	
	SQV FCT/RTV	3924	119.07	[113.67, 124.72]

Reviewer Comment: The new SQV FCT formulation achieves similar BA as the current marketed formulation SQV HGC when both SQV formulations are administered with low dose RTV under fed conditions.

A gender effect with SQV PK was noted in the BP17359 study subjects, with the female subjects achieving higher SQV exposures (AUC ↑56% and C_{max} ↑26%) compared to the male subjects. Unfortunately, the sample size of female subjects in BP17359 was very small as compared to the males (N=7 females and N=93 males), and this makes the interpretation difficult. No increase in adverse events (ADEs) reporting was seen in females as compared to males enrolled in the study. The gender effect seen in BP17359 has been reported in other SQV studies in the literature (MaxCmin, ACTG-359 and BP17653) and it's hypothesized to be related to the differing amounts of CYP3A4 enzyme and p-glycoprotein (PGP) in females compared to males. With the large variability seen in SQV concentrations (both genders), the interpretation of the data relative to gender effect is difficult to translate into a meaningful clinical effect (safety or efficacy).

Assessment/Conclusion

1. The new SQV FCT formulation achieves similar BA compared to the current marketed formulation SQV HGC, when both SQV formulations are administered with low dose RTV under fed conditions.
2. A gender effect is present with SQV PK in BP17359, with female subjects achieving higher SQV exposures (AUC ↑56% and C_{max} ↑26%) compared to the male subjects.
3. Due to the large inter-subject variability seen in SQV concentrations for both male and female subjects, along with the small number of female subjects enrolled into BP17359, the gender effect reported in BP17359 is difficult to translate into a meaningful clinical effect in safety or efficacy.

4.1.3 Pivotal Bioequivalence (BP17653)

The applicant has developed a new 500-mg film-coated tablet (FCT) formulation of saquinavir mesylate (SQV), which is the same salt found in Invirase® Hard Gel Capsule. In a previously conducted pivotal relative bioavailability (BA) study (BP17359), the new Invirase® FCT formulation had similar BA compared to Invirase® HGC, when co-administered with low dose ritonavir (RTV) under fed conditions.

At the Agency's request, the applicant conducted a pivotal BE study (BP17653) to assess the SQV exposure of the new SQV FCT formulation (test product) relative to the current marketed HGC formulation (reference product) after administration of SQV alone under fed conditions.

Study Design
This was a single-center, open-label, randomized, two-sequence, four-period, two-treatment, replicated, crossover study conducted in 20 healthy adult subjects under fed conditions. Each subject was randomized to one of two different sequences (ABAB or BABA). On PK days (Days 1, 4, 7, and 10), a standard high fat breakfast was administered prior to study drug administration. The table below provides a description of how study drugs were administered.

Table 1. Overview of Study Design

Screening	Period 1 First Dose*	Period 2 Second Dose*	Period 3 Third Dose*	Period 4 Fourth Dose*	Follow-Up Visit
Day -28 to Day -1	Day 1	Day 4**	Day 7**	Day 10**	Day 25 to Day 31

***Single dose of SQV as per randomization sequence**
****Washout period of 2-days**

Study Treatments
Treatment A (Reference Treatment): Invirase® HGC 1000-mg (5 x 200-mg)
Treatment B (Test Treatment): Invirase® FCT 1000-mg (2 x 500-mg)

Table 2. Study Medication

Drug	Strength	Dosage Form	Batch Number
Invirase® FCT	500-mg	Tablet	PT9511B34
Invirase® HGC	200-mg	Capsule	B1132

Meal Composition

Table 3. Standard High Fat Breakfast

Food	Quantity	Protein (grams)	Lipids (grams)	CHO (grams)
Whole Milk	227 mL	7.49	19.98	10.67
Eggs	2 eggs	12.5	11	2
Butter	15 grams	0.07	12.3	0
Gruyere Cheese	30 grams	8.82	8.64	0.06
Sandwich Loaf	2 slices	3.12	1.17	21.06
Hash Browns	2 pieces	3.6	10	32.4
Total (grams)		35.6	63.09	66.19
Calories (kcal)		142.4	567.81	264.76
Calories (%)		14.6	58.2	27.2

Total Calories: 975

Study Demographics

Table 4. Summary of Demographics

Sex:	
Male	10 (50%)
Female	10 (50%)
n	20
Race:	
Caucasian	20 (100%)
Black	-
Oriental	-
Other	-
n	20
Age:	
Mean	43.2 yr
SD	11.61
Weight:	
Mean	69.46 kg
SD	15.53
Height:	
Mean	168.3 cm
SD	9.66

Data Source: Applicant's Module 5, Volume 13 page 32

PK Sampling

Venous blood samples were collected to measure SQV concentrations at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours after SQV administration on Days 1, 4, 7, and 10.

PK Analysis

PK parameters were calculated using WinNonlin (Version 4.0.1) non-compartmental methods. The following PK parameters of SQV were calculated for each subject from the concentration time data obtained during the PK sampling: C_{max}, t_{max}, $t½$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and CL/F.

- All pharmacokinetic parameters for testing the BE were analyzed using analysis of variance (ANOVA).
- For the assessment of the formulation BE, a 90% CI was obtained for the geometric mean ratio (Treatment A as reference product and Treatment B as test product).
- BE was concluded if the 90% CI intervals were within the 80-125% range for C_{max} and AUC.

BP17653 Assay Validation

Table 5. Synopsis of Bioanalytical Report

Protocol Number	BP17653
GLP	Yes
Sample Origin	BP17653 Study
Species	Human
Biological Material	Plasma
Analytical Method	[redacted] HPLC with tandem mass spectrometric detection
Sensitivity of Assay	[redacted]
Precision (%CV)	[redacted]
Accuracy	[redacted]

Reviewer Comment: The assay is acceptable.

BP17653 Study Results

The summary statistics of SQV FCT and SQV HGC PK parameters are listed in the table below.

Table 6. PK Parameters [Mean (CV)] of SQV after Treatment with Invirase® (HGC) and Invirase® (FCT)

Parameter	Treatment A: HGC	Treatment B: FCT
Number of observations	40	40
$AUC_{0\text{-}inf}$ (ng·h/mL):		
Arithmetic Mean	1192 (49%)	1514 (62%)
Geometric Mean	1062	1235
C_{max} (ng/mL)		
Arithmetic Mean	348 (75%)	404 (58%)
Geometric Mean	285	332
t_{max} (h)		
Median	4.37	3.88
(min, max)	(1.00,10.00)	(1.02,6.00)
t½ (h)		
Arithmetic Mean	8.29 (36%)	7.73 (26%)
Geometric Mean	7.89	7.51
CL/F (mL/min)		
Arithmetic Mean	1080 (63%)	1059 (91%)
Geometric Mean	941	809

Data Source: Applicant's Module 5, Volume 12 page 34

The geometric least square means (GLS) and 90% CI values for SQV FCT and SQV HGC are listed in the table below.

Table 7. Estimated Mean Exposures and Estimated Mean Exposure Ratios (90% Confidence Interval) for SQV [N= (10 Females + 10 Males) x 4 PK Profiles]

PK Parameter	Treatment	Est. Mean Exposure[a]	Est. Mean Exposure Ratio	90% CI
$AUC_{0\text{-}inf}$ (ng·h/mL)[b]:	**Females:**			
	SQV HGC	1086		
	SQV FCT	1485	1.37	[1.17, 1.59]
	Males:			
	SQV HGC	1039		
	SQV FCT	1028	0.99	[0.85, 1.15]
C_{max} (ng/mL)	**Females:**			
	SQV HGC	306		
	SQV FCT	395	1.29	[1.03, 1.62]
	Males:			
	SQV HGC	265		
	SQV FCT	278	1.05	[0.84, 1.31]
	All:			
	SQV HGC	285		
	SQV FCT	332	1.16	[0.99, 1.37]

a: exponential least square means of ln-transformed exposure parameters
b: overall estimation of mean exposures and exposure ratios for the two treatments not provided due to the finding of a gender by treatment interaction
Data Source: Applicant's Module 5, Volume 12 page 11

Reviewer Comment: The new SQV FCT formulation is not BE to the current marketed SQV HGC when administered alone under fed conditions. The $AUC_{0\text{-}inf}$ and C_{max} values achieved by both SQV formulations in this study were approximately 20 to 25-fold less and 10 to 15-fold less compared to the $AUC_{0\text{-}inf}$ and C_{max} values reported in the pivotal relative BA study BP17359 when SQV was administered with low dose RTV. The inter-subject variability values were much higher in this study when compared to the values reported in BP17359 (AUC 49% to 79% compared to 45% to 50% and C_{max} 58% to 79% compared to 38% to 42%). This study was conducted under fed conditions because of the well documented poor BA (approximately 4%) and large inter- and intra-subject variability associated with SQV exposures. When SQV is taken with food, the BA and variability is improved. Therefore, conducting SQV BA or BE studies under fed conditions is agreed upon by the Agency.

There was evidence of a difference in the relative performance of the two SQV formulations between male and female healthy volunteers with respect to the $AUC_{0\text{-}inf}$ of SQV. For female subjects, a mean exposure ratio of SQV FCT vs. SQV HGC for $AUC_{0\text{-}inf}$ was 1.37 [90% CI: 1.17, 1.59] and for male subjects 0.99 [90% CI: 0.85, 1.15]. This difference is caused by a higher mean $AUC_{0\text{-}inf}$ value reported for the SQV FCT formulation when administered to females as compared to the mean $AUC_{0\text{-}inf}$ value reported for the SQV HGC formulation in females (1485 vs. 1086 ng·h/mL). Because of this gender by treatment finding for $AUC_{0\text{-}inf}$ values, an overall (both male and female study subjects) estimation of mean exposures and exposure ratios for the two treatments was not conducted by the applicant. The C_{max} values reported did not indicate such a difference in the relative performance of the two formulations between genders even though females in general achieved higher C_{max} values compared to the

male study subjects. These findings are not considered clinically significant because SQV FCT will not be administered alone as a sole PI. In addition, this formulation performance difference was not duplicated in BP17359 where SQV FCT was administered with low dose RTV, the intended way SQV FCT will be administered upon its approval.

Assessment/Conclusion

1) The new SQV FCT formulation is not BE to the current marketed SQV HGC. The SQV FCT achieves higher concentrations compared to the SQV HGC.
2) Inter-subject variability is increased when SQV (either formulation) is given without low dose RTV.

4.2 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	**21-785**	**Sponsor:**	**Hoffmann La Roche**
IND:	41,099		
Brand Name:	INVIRASE FILM-COATED TABLETS 500-mg	**Priority Classification:**	P1
Generic Name:	Saquinavir Mesylate 500-mg Tablet	**Indication(s):**	Treatment of HIV-Infection
Drug Class:	Protease Inhibitor	**Date of Submission:**	18June2004
Dosage Form:	Tablets	**Route of Admin.:**	Oral
Dosing Regimen:	Saquinavir 1000-mg + 100-mg Ritonavir BID	**Due Date of Review:**	15Dec2004
Division:	DPEIII	**Medical Division:**	HFD-530
Reviewer:	J. L. DiGiacinto	**Team Leader:**	K. S. Reynolds

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies			
Mass Balance Study		X	
BA Studies			
Absolute BA		X	
Relative BA	X		
BE Studies			
Average BE	X		
Population BE		X	
Individual BE		X	
Food-Drug Interaction		X	
Dissolution Tests (In Vitro-In Vivo Comparison Studies)	X		
Studies Using Human Biomaterials			
Plasma Protein Binding Studies		X	
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc		X	
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies			
PK, and Initial Safety and Tolerability in Healthy Volunteers			
Single Dose		X	
Multiple Dose		X	
PK, and Initial Safety and Tolerability in Patient Volunteers			
Single Dose		X	

Multiple Dose		X	
Dose Proportionality			
Single Dose		X	
Multiple Dose		X	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors			
Ethnicity		X	
Gender		X	
Pediatrics		X	
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors			
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies		X	
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers		X	
PK/PD studies in patients		X	
Individual Datasets for all PK and PK/PD studies in electronic format		X	
Other			
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	
Literature References		X	

This application is √ is not ___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)
Are there any outstanding issues or concerns raised in NDA 21-785 that have not been adequately addressed by the applicant? No

Requests/Comments are ___ are not ___ to be sent to firm. If any was sent, indicate the date of FDA letter.
PM Consult

Signature _____ _____

Primary Reviewer **Secondary Reviewer**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jennifer DiGiacinto
12/14/04 10:40:15 AM
BIOPHARMACEUTICS

Kellie Reynolds
12/14/04 11:28:17 AM
BIOPHARMACEUTICS