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*APPLICATION NUMBER:*

**21-785**

**STATISTICAL REVIEW(S)**

## JOINT CLINICAL AND STATISTICAL REVIEW

Application Type NDA  
Submission Number 21-785  
Submission Code N-000

Letter Date June 17, 2004  
Stamp Date June 22, 2004  
PDUFA Goal Date December 17, 2004

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Review Completion Date December 13, 2004

Established Name Saquinavir Mesylate  
(Proposed) Trade Name INVIRASE®  
Therapeutic Class Antiretroviral Agent  
Applicant Hoffman-La Roche, Inc.

Priority Designation P

Formulation 500 mg Film-Coated Tablets  
Dosing Regimen 1000 mg BID (co-administered  
with ritonavir 100 mg BID)  
Indication Treatment of HIV Infection  
Intended Population  $\geq 16$  years of age

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

Saquinavir (SQV), an inhibitor of the HIV-encoded protease, has previously been approved by the Agency as a mesylate salt in hard-gelatin capsules (HGC) called Invirase® (INV HGC) and as a soft-gel capsule (SGC) formulation called Fortovase® (FTV). In December 2003, the dosing regimen of 1000 mg SQV (dosed as either INV HGC or FTV) twice daily with co-administration of ritonavir (RTV) 100 mg BID was approved to treat HIV infection in combination with other antiretroviral agents. INV HGC is no longer to be used as a sole PI in an antiretroviral regimen to treat HIV infection.

Currently, patients on RTV-boosted SQV regimens are still confronted with a relatively high pill burden of six capsules (five of FTV or INV HGC with one for RTV) to be taken twice daily in addition to other antiretroviral agents. To further reduce the pill burden and thus improve patient compliance and tolerability, the applicant has developed a new formulation of saquinavir mesylate as Invirase® 500 mg film coated tablets (INV FCT).

In this NDA, the applicant provides pharmacokinetic data from three healthy volunteer studies to show the relative bioavailability and bioequivalence of INV FCT to INV HGC. To address possible safety concerns due to increased SQV exposure among female subjects, the applicant has provided safety and limited pharmacokinetic data from two clinical studies in HIV-infected subjects.

Based on the review of this NDA, it is the collective opinion of the Clinical and Statistical Reviewers that the INV 500 mg FCT should be approved. No significant deficiencies that preclude the approval of this NDA are identified. Based on its pharmacokinetic properties, INV FCT is expected to have an efficacy profile that is similar to that of INV HGC. The benefit of decreased pill burden to improve tolerability and compliance to antiretroviral treatment outweigh the risks of SQV-associated adverse events; based on this notion, this NDA was considered under a Priority Review. At this time, no formal changes in the product label are requested regarding possible gender effects on SQV exposure and safety profile; the applicant will be asked to address these issues in greater detail as postmarketing commitments.

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

No specific Risk Management Activities have been discussed with or requested from the applicant.

### 1.2.2 Required Phase 4 Commitments

Based on the review of data in this NDA, the following postmarketing commitments are requested by the Division:

- Conduct a retrospective analysis on the effects of gender on the safety profile of SQV 1000 mg /RTV 100 mg. Safety data should be provided from at least 50-100 female participants with appropriately matched comparative data from male subjects.
- Conduct a safety analysis by gender and saquinavir levels for subjects who received SQV 1000 mg/RTV 100 mg and were enrolled in the pharmacokinetic substudies of the MaxCmin 1 and MaxCmin 2 studies. Data from the two studies should be pooled for analysis and a uniform adverse event coding system should be used.
- Determine the baseline genotype of all PI-experienced responders in the MaxCmin 1 and MaxCmin 2 studies and submit in the resistance template format. Resubmit MaxCmin 1 and MaxCmin 2 failure dataset with a column identifying isolate (specifically “baseline”) and with a column identifying outcome (nonresponder, rebound, censored, etc.)

The Final Study reports for the first two postmarketing commitments are to be forwarded to the Agency within 12 months of the action date for this NDA. The Final Report for the third postmarketing commitment is to be forwarded to the Agency within six months of the action date for this NDA.

### 1.2.3 Other Phase 4 Requests

Aside from those listed in the previous section, no other Phase 4 commitments are requested from the applicant.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

In this NDA, data from three pharmacokinetic studies in healthy volunteers are presented:

1. BP17058 (bioavailability study comparing bioavailability of INV FCT vs. INV HGC without RTV);
2. BP17359 (bioequivalence study of INV FCT + RTV vs. INV HGC + RTV); and
3. BP17633 (bioavailability study of INV FCT + RTV vs. INV HGC + RTV).

In addition, the applicant states that there may be increased SQV exposure in female subjects as compared to male subjects. To address potential safety concerns arising from increased SQV exposure and/or gender effects, the applicant provides safety and limited pharmacokinetic data from two studies in HIV-infected subjects:

1. NR15720 (SQV as FTV 1600 mg/ RTV 100 mg once daily with two NRTIs); and

2. MaxCmin 1 (SQV as FTV 1000 mg/RTV 100 mg BID with two additional antiretroviral agents). This study was reviewed with regards to safety and efficacy to support the approval of the SQV 1000 mg/RTV 100 mg BID dosing regimen in December 2003.

### 1.3.2 Efficacy

No efficacy data were reviewed for the approval of this NDA. Based on the pharmacokinetic parameters of INV FCT as compared to INV HGC, the INV FCT is expected to have an efficacy profile that is similar to previously approved SQV formulations.

### 1.3.3 Safety

The three PK studies in healthy volunteers were reviewed for safety. Data from BP15058 and BP15359, in which subjects received RTV-boosted SQV, were pooled by the applicant for this review. The AE profile of SQV as demonstrated in these three studies was consistent with that previously associated with SQV and/or RTV use.

In the two studies in HIV-infected patients, the safety profile of subjects who received SQV/RTV were also reviewed for safety with specific emphasis on the possible effects of SQV  $C_{min}$  and gender. It should be noted that the MaxCmin 1 study was reviewed in December 2003 for safety and efficacy. For this review process, revised datasets from this study bearing MedDRA coded AEs were re-analyzed by the Clinical and Statistical Reviewers. For both studies, Week 4 SQV  $C_{min}$  levels were provided for a subset of subjects.

In the NR15720 study, male and female subjects in the pharmacokinetic substudy had similar Week 4 SQV  $C_{min}$  levels and also had similar adverse event profiles. In the MaxCmin 1 study, the mean SQV  $C_{min}$  level for female subjects ( $n = 15$ ) was approximately 1.6 fold higher than that for male subjects ( $n = 54$ ). Moreover, in the MaxCmin 1 study, female subjects reported a higher median number of adverse events (all body systems and those involving the gastrointestinal system) and in general, experienced a shorter time to onset of such adverse events as compared to male subjects. However, the applicant states that there was no obvious correlation between Week 4 SQV  $C_{min}$  levels and the frequency, type, and/or intensity of adverse events. With regard to laboratory parameters, in both studies, the applicant notes that there was no evidence that increased SQV  $C_{min}$  levels were correlated with organ system function, including hepatic function.

In general, these findings were confirmed by the Clinical and Statistical Reviewers. However, several limitations of the pharmacokinetic substudies, such as the relatively small number of female subjects, the use of FTV, the heterogeneous nature of the patient population with respect to baseline factors (e.g. history of antiretroviral treatment), are noted by the Reviewers. Thus, at this time, no formal changes in the product label are requested regarding possible gender effects on SQV exposure and safety profile; the applicant will be asked to address these issues in greater detail as postmarketing commitments.

#### 1.3.4 Dosing Regimen and Administration

The recommended dosing regimen for INV FCT is 1000 mg to be taken orally with RTV 100 mg BID, which is identical to that approved in December 2003 for INV HGC and FTV. The dosing regimen is supported by pharmacokinetic studies in this NDA.

#### 1.3.5 Drug-Drug Interactions

Drug interactions with SQV were most recently reviewed in December 2003 for the approval of 1000 mg FTV or INV HGC/100 mg RTV BID dosing regimen. As postmarketing commitments, the applicant is in the process of fulfilling drug interaction studies of SQV/RTV 1000 mg/100 mg BID with efavirenz, ketoconazole, methadone, and rifampicin. No new drug interactions involving SQV are presented in this NDA. Please see Dr. DiGiacinto's ClinPharm Review for additional details.

#### 1.3.6 Special Populations

In this NDA, no new dosing considerations for special populations are included. Please see Sections 8.2 and 8.4 for additional details on further studies in patients with hepatic impairment and pediatric patients.

The pediatric Written Request for SQV has been resubmitted in November 2004. Study reports for the fulfillment of this Written Request are to be submitted to the Agency on or before March 31, 2006.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Trade (Generic) names for the proposed product for approval in this NDA:  
Invirase® (saquinavir mesylate) 500 mg film coated tablets.

Trade (Generic) names of previously approved dosage forms:  
Invirase® (saquinavir mesylate): 200 mg hard gel capsules, previously approved in 1995.  
Fortovase® (FTV; saquinavir): 200 mg soft gel capsules, previously approved in 1997.

Chemical names:

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS, 8aS)-isoquinoline-3(S)-carboxamide (saquinavir) and its methanesulfonate (saquinavir mesylate).

Chemical class:

New dosage formulation (500 mg film coated tablets; abbreviated as FCT throughout this review).

Pharmacological class: Antiretroviral agent (protease inhibitor; PI).

Proposed dosing regimen: 1000 mg BID to be co-administered with ritonavir 100 mg BID.

Proposed indication: Treatment of HIV-infected adults and adolescents over the age of 16 years.

Saquinavir (SQV) is an inhibitor of the HIV-encoded protease. Because of its mechanism of action, SQV prevents the formation of infectious virions from HIV-infected cells. For treatment of HIV infection in combination with other antiretroviral agents, SQV was approved by the Agency in 1995 as a mesylate salt formulation in hard-gelatin capsules (HGC) called Invirase® (abbreviated as INV HGC throughout this review). In 1997, a soft-gel capsule (SGC) formulation of SQV called Fortovase® (SQV base dissolved in the excipient Capmul; abbreviated as FTV throughout this review) was approved by the Agency for the same indication. Both INV HGC and FTV were initially approved for use in thrice-daily dosing regimens.

Over the last several years, co-administration of FTV or INV HGC with another PI, ritonavir (RTV; Norvir®, Abbott Laboratories) has been used in clinical practice to treat HIV infection. When RTV is administered as 100 mg BID, it does not significantly suppress HIV replication but will inhibit the p-glycoprotein-dependent SQV transport in the gastrointestinal tract and the CYP3A4-dependent metabolism of SQV. Thus, when administered with FTV or INV HGC, RTV increases (“boosts”) patient exposure to SQV. In December 2003, the dosing regimen of 1000 mg SQV (dosed as either INV HGC or FTV) twice daily with co-administration of RTV

100 mg BID was approved to treat HIV infection in combination with other antiretroviral agents. INV HGC is no longer to be used as a sole PI in an antiretroviral regimen to treat HIV infection.

As compared to the thrice daily FTV regimen, RTV-boosted SQV regimens enable twice daily administration of FTV or INV HGC and thus are expected to improve patient compliance. However, patients on RTV-boosted SQV regimens are still confronted with a relatively high pill burden of six capsules (five of FTV or INV HGC with one for RTV) to be taken twice daily in addition to other antiretroviral agents. To further reduce the pill burden and thus improve patient compliance and tolerability, the applicant has developed a new formulation of saquinavir mesylate as Invirase® 500 mg film coated tablets (abbreviated as INV FCT throughout this review).

In this NDA, the applicant seeks approval of INV FCT based on three pharmacokinetic (PK) studies to show relative bioavailability and bioequivalence with the existing SQV formulations when dosed with RTV 100 mg BID. With respect to INV FCT, no efficacy or safety data specific to this formulation are presented.

In the safety analysis in this NDA, the applicant addresses a recently identified gender-related effect on SQV exposure (Fletcher, C.V., et al., Sex-based differences in saquinavir pharmacology and virologic response in AIDS Clinical Trials Groups Study 359. *J. Infect. Dis.* 189: 1176-1184, 2004). In this publication, the authors show that female subjects in the ACTG 359 study had higher SQV AUC and  $C_{min}$  values than did male subjects. Correspondingly, a greater proportion of female subjects had HIV RNA levels  $\leq$  500 copies/mL than did male subjects. To determine whether or not gender or SQV exposure levels are associated with alterations in the safety profile for SQV, the applicant presents limited PK substudies from two clinical studies in HIV-infected patients. These are reviewed in detail in the Integrated Review of Safety.

This review was written jointly by the Medical Officer (Y. Murata, M.D., Ph.D.) and the Statistical Reviewer (S. Zhou, Ph.D.). The Statistical Reviewer wrote specific sections in the safety analyses of NR15720 and MaxCmin 1 studies, including those regarding the PK substudy population and AE analysis by gender. Graphs and tables prepared by the Statistical Reviewer are included in the review. The Medical Officer wrote the majority of this Clinical/Statistical Review and was primarily responsible for the synthesis of conclusions with consultative opinions provided by the Statistical Reviewer.

## 2.2 Currently Available Treatment for Indications

As of this writing, there are four classes of drugs that have been approved to treat human immunodeficiency virus (HIV) infection: 1) nucleoside reverse transcriptase inhibitors (NRTIs); 2) non-nucleoside reverse transcriptase inhibitors (NNRTIs); 3) protease inhibitors (PIs); and 4) fusion and attachment inhibitors. The current standard of care for HIV infections is the simultaneous administration of three or more antiretroviral agents to reduce viral replication while minimizing the risk of viral resistance.

### **2.3 Availability of Proposed Active Ingredient in the United States**

FTV and INV HGC are currently approved for use in the United States. Please see Section 2.2 for additional details on the regulatory experience and recent labeling changes, including dosing recommendations that were approved in December 2003.

### **2.4 Important Issues With Pharmacologically Related Products**

Since the advent of PIs as a treatment option for HIV, it has been shown that the effectiveness of PIs as well as other antiretroviral agents may be severely compromised by emergence of viral resistance. The Microbiology sections of FTV and INV HGC product labels were updated in December 2003 to contain most current information of HIV resistance to SQV.

Several safety issues have been identified through clinical experience with PIs. Such issues include diabetes mellitus, hyperglycemia, fat redistribution, and drug interactions (e.g. with garlic capsules, St. John's Wort, and HMG-CoA reductase inhibitors). In December 2003, the product labels for INV and FTV were updated to contain the most current Precautions and Warnings on safety-related issues that are present in product labels of other PIs. In this NDA, the applicant does not propose any new agent- or class-specific warnings.

### **2.5 Presubmission Regulatory Activity**

A pre-NDA teleconference package dated March 26, 2004 was submitted to the Division of Antiviral Drug Products ("DAVDP") under IND 41,099 for INV HGC. This package was reviewed by DAVDP and discussed with the applicant during a pre-NDA teleconference on May 21, 2004. During this teleconference, the following agreements were reached between the DAVDP and the applicant:

- DAVDP agreed that the demonstration of bioequivalence of the INV FCT with INV HGC in study BP 17359 and the supporting relative bioavailability data from studies BP 17058 and BP 17653 were adequate to support the filing of this NDA.
- DAVDP agreed with the applicant's proposal that the filing of this NDA will qualify for a priority review given the reduction in pill burden of patients requiring therapy with SQV.
- The format and the contents of the NDA were agreed upon, including cross-referencing of the MaxCmin 1 study report (previously filed under supplemental NDAs 20628 and 20828 that were approved in December, 2003) and CMC dissolution data on the INV FCT.
- In this NDA, the applicant requested a deferral for pediatric studies in patients with HIV infection. Pediatric development of SQV was subsequently discussed during a face-to-face meeting between the applicant and DAVDP on June 30, 2004. Following this meeting, the pediatric written request for SQV has been rewritten in November, 2004 (see Section 8.4).

## **2.6 Other Relevant Background Information**

# **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

## **3.1 CMC (and Product Microbiology, if Applicable)**

With respect to Microbiology, the product label for INV FCT will include updated information on the activity of SQV on non-clade B strains of HIV-1 and viral resistance against SQV. Please refer to Dr. Battula's Microbiology review for additional details.

Based on preliminary discussions with Dr. Lorenzo Rocca, the CMC Reviewer, there are no clinically significant CMC findings in this NDA. Please refer to Dr. Rocca's CMC review for additional details.

## **3.2 Animal Pharmacology/Toxicology**

No new Pharm/Tox issues are identified or presented in this NDA. Please refer to Dr. Wu's PharmTox review for additional details, including minor changes to the PharmTox section of the proposed INV FCT label.

# **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

## **4.1 Sources of Clinical Data**

This NDA is comprised of 28 volumes in paper submission format that contain the clinical reports for the three PK studies in healthy volunteers and one of two clinical studies (NR15720) in HIV-infected subjects. In addition, the applicant cites the December 2003 approval of supplemental NDAs 20628/20828 for the final study report of the other clinical study (MaxCmin 1) that was conducted in HIV-infected subjects. Also included in the paper volumes are the relevant reports to be reviewed by other disciplines, including ClinPharm and CMC, as well as literature reprints to assist in the review process.

In support of this NDA, the applicant has submitted electronic datasets bearing clinical pharmacology and safety data from the five clinical studies listed in Section 4.2, below. During the course of the review process, updated electronic datasets bearing re-coded adverse events from the MaxCmin 1 study was submitted by the applicant on August 2004.

In December 2003, a consultation report was requested by the DAVDP to the Office of Drug Safety (ODS) regarding postmarketing adverse events associated with co-administration of SQV and RTV. During the review process, this consultation report was reanalyzed to ensure that no significant gender effects were noted among a subset of clinically significant adverse events (see Section 7.1.17, below).

#### 4.2 Tables of Clinical Studies

The applicant provides the following table to summarize the five studies in this NDA:

Table 1. Summary of Clinical Studies in this NDA.

Study #	Study Objectives	Study Design	Treatments	Subject/Patient #, type
BP17058	Bioavailability INV FCT 500 mg vs. INV HGC 200 mg	Open-label, single-dose, randomized, 2-sequence, 4-period, 2-treatment, replicated crossover	INV FCT 1000 mg + RTV 100 mg po BID vs. INV HGC 1000 mg + RTV 100 mg po BID	20 healthy male volunteers, mean age: 30 (19-56)
BP17359	Bioequivalence INV FCT 500 mg vs. INV HGC 200 mg	Two-center, open label, single dose, randomized, 2-sequence, 4-period, 2-treatment, replicated crossover	INV FCT 1000 mg + RTV 100 mg po BID vs. INV HGC 1000 mg + RTV 100 mg po BID	100 healthy volunteers, 93 male, 7 female, mean Age: 37 (19-65)
BP17633	Bioavailability INV FCT vs. INV HGC 200 mg	Open-label, single dose, randomized, 2-sequence, 4-period, 2-treatment, replicated crossover	INV FCT 1000 mg vs. INV HGC 1000 mg	20 healthy volunteers, 10 male, 10 female, mean age: 43 (20-64)
NR15720 (FOCUS)	Primary: virologic response Secondary: virological and immunological response, safety, pharmacokinetics.	Randomized, open-label, multi-center, 48 weeks	ARM A: SQV (FTV) 1600 mg + RTV 100 mg QD + 2 NRTIs ARM B: EFV 600 mg + RTV 100 mg QD + 2 NRTIs	171 randomized subjects ARM A: 86 ARM B: 85
MaxCmin 1	Primary: Virological failure in indinavir/RTV arm relative to the SQV/RTV arm Secondary: Immunological and virological response, safety, genotypic and phenotypic resistance, pharmacokinetics	Randomized, open-label, multi-center, 48 weeks	ARM A: FTV 1000 mg + RTV 100 mg BID + 2 NRTIs/NNRTIs ARM B: Indinavir 800 mg + RTV 100 mg BID + 2 NRTIs/NNRTIs	317 randomized subjects ARM A: 158 ARM B: 159

Source: NDA 21,785, Module 2, Volume 1, p. 59-63.

### **4.3 Review Strategy**

No new efficacy data are provided in this NDA. Please refer to the ClinPharm review by Dr. DiGiacinto for the review of three PK studies in healthy volunteers to demonstrate the relative bioequivalence and bioavailability of the INV FCT with respect to INV HGC.

In this Clinical/Statistical Review, the five clinical studies listed in Table 1 were reviewed for safety. The MaxCmin 1 study was reviewed for efficacy and safety in December 2003; the previous efficacy review with regard to gender is summarized in Section 6. No new efficacy data are reviewed in this study. The safety and efficacy of the comparator arm in NR15720 was not reviewed, and those of the comparator arm for MaxCmin 1 have been reviewed previously.

For this NDA, the safety of SQV/RTV dosing regimens used in studies NR15720 and MaxCmin 1 was determined among all subjects who received SQV/RTV and also those for whom Week 4 plasma SQV  $C_{\min}$  levels were available. These data were reviewed to determine whether or not the increased SQV exposure and/or gender was associated with changes in the safety profile for SQV.

For the joint Clinical/Statistical Review process, the Medical Officer was primarily responsible for the synthesis and documentation of the overall conclusions for the application as well as providing primary reviews of AEs, SAEs, and deaths. This Medical Officer also prepared the summaries of all five studies, including study design, inclusion/exclusion criteria, and study demographics, that are present in the Appendix of this Clinical/Statistical Review. The primary statistical analyses of data, including laboratory values, as well as the effects of gender and SQV exposure on the safety profile of SQV, were performed by the Statistical Reviewer using the applicant's datasets and SAS 8.1.

### **4.4 Data Quality and Integrity**

Following internal discussion within DAVDP and the Clinical Review Team for this NDA, audits or site visits by the Division of Scientific Investigations were not requested.

### **4.5 Compliance with Good Clinical Practices**

The study reports for the three PK studies and that for NR15720 are included in the paper submission volumes for this NDA. The final study report for the MaxCmin 1 study was submitted in February 2003 and reviewed in December 2003. Each of the five study reports contains assurances that the respective study was conducted in accordance with acceptable ethical standards and informed consent was appropriately obtained. No significant protocol violations or site-specific issues are described in any of the study reports.

### **4.6 Financial Disclosures**

In this NDA, the applicant has submitted a signed copy of Form FDA 3454. Based on the information contained on this form, the applicant has adequately disclosed financial

arrangements with clinical investigators. Based on such disclosure, no significant questions were raised by this Medical Officer regarding the integrity of data presented in this NDA.

## **5 CLINICAL PHARMACOLOGY**

### **5.1 Pharmacokinetics**

The PK parameters of SQV (as FTV or INV HGC) have been reviewed during the previous regulatory approval processes and have been extensively described in the medical literature. The product labels for INV HGC and FTV were updated in December 2003 to indicate drug interactions based on the co-administration regimens of SQV 1000 mg with RTV 100 mg.

Of the three PK studies that were submitted in this NDA, two pivotal studies (BP17359, the relative bioavailability study and BP17653, the pivotal bioequivalence study) were reviewed by the ClinPharm team to show bioavailability and bioequivalence, respectively, of the INV FCT and INV HGC. BP17058 was considered by the ClinPharm team to be a pilot scale study which enrolled only male participants. Please see Dr. DiGiacinto's ClinPharm review for additional details.

### **5.2 Pharmacodynamics**

The pharmacodynamic effects of SQV on HIV RNA levels have been well characterized in clinical practice and extensively described in the medical literature. No new pharmacodynamic findings on SQV are presented in this NDA.

### **5.3 Exposure-Response Relationships**

No new exposure-response relationships regarding SQV are presented in this NDA. For safety analysis with respect to SQV exposure, please see Section 7, Integrated Review of Safety section of this review.

## **6 INTEGRATED REVIEW OF EFFICACY**

The indication that is sought by the applicant for INV FTC is for the treatment of HIV infection in combination with other antiretroviral agents. No new efficacy data based on the use of INV FCT are presented in support of this indication. Based on the ClinPharm review of bioavailability/bioequivalence of INV FTC to INV HGC, the efficacy profile of INV FCT is expected to be similar to that for INV HGC.

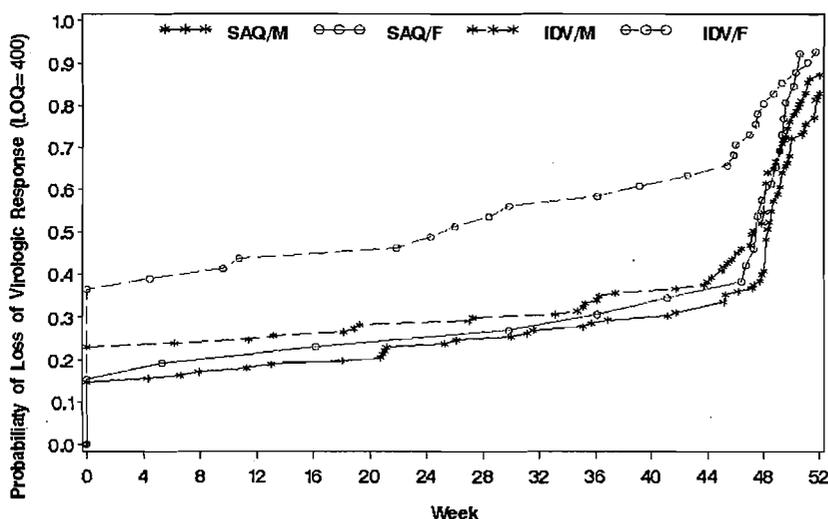
The efficacy of SQV (as FTV) 1000 mg/RTV 100 mg BID regimen as demonstrated in the MaxCmin 1 study was reviewed by the Statistical Reviewer in December 2003. During the previous review process, the efficacy of the SQV/RTV regimen was examined by this Statistical Reviewer for possible gender effects to identify confounding or covariate factors with statistical

significance. The following section is derived from the Statistical Reviewer’s previous efficacy analyses of the MaxCmin 1 data (Zhou, 2003).

A larger level of statistical significance ( $p < 0.20$ ) was used for the examination of statistical interaction of possible covariate factors. The TLOVR dataset generated with LOQ = 400 copies/mL was used for analyses and the outcome measurement was virologic response through Week 48. The number of responders and non-responders at Week 48 (cutpoint = study day 294) by treatment regimen and covariate strata were obtained as binary outcomes for the quantitative evaluations.

Figure 1 shows the proportions of non-responders through Week 48 by treatment regimens and gender for LOQ = 400 copies/mL. Overall,  $p = 0.0084$  was obtained by the log-rank test. Of note, 22% of all study subjects were female.

Figure 1: MaxCmin 1: Efficacy Analysis by Gender and TLOVR (LOQ = 400 copies/mL).



Note: SAQ/M and SAQ/F refer to male and female subjects, respectively, who received SQV/RTV. Similarly, IDV/M and IDV/F refer to male and female subjects, respectively, who received the comparator regimen of indinavir/RTV.

Source: NDA 20,628/20,828 Agency analysis, December 2003 (Zhou, 2003).

Table 2 summarizes the gender difference in virologic response rates and 95% CI by treatment regimen and vice versa. Based on the subgroup comparisons in virologic response rates at Week 48 using the Wald t-test, for female subjects, there was a significant treatment difference in virologic response rates (between treatment arms) at Week 48 (26.4 %,  $p < 0.05$ ). The lack of significant gender effect on the efficacy of SQV/RTV as used in this study is shown in bold.

Table 2: MaxCmin 1: Summary of Gender and Treatment Differences in Response Rate (%) using TLOVR Algorithm at Week 48<sup>1</sup>

Gender	Male	Female	Male-Female <sup>2</sup>	95% CI
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<b>SQV/RTV (N=148)</b>	<b>68.9</b>	<b>65.4</b>	<b>3.5 (10.1)</b>	<b>-16.2, 23.2</b>
<b>IDV/RTV (N=158)</b>	63.3	39.0	24.2 (9.0)	6.6, 41.8 <sup>3</sup>
<b>Treatment</b>	<b>SQV/RTV</b>	<b>IDV/RTV</b>	<b>SQV/RTV - IDV/RTV<sup>2</sup></b>	<b>95% CI</b>
<b>Male (N=239)</b>	68.9	63.3	5.6 (6.1)	-6.4, 17.6
<b>Female (N=67)</b>	65.4	39.0	26.4 (12.5)	1.8, 50.9 <sup>3</sup>

1: LOQ = 400 copies/mL and the low bound of Week 48 is 42 weeks since baseline.

2: Standard error of the difference in virologic response rates at Week 48 in parentheses.

3:  $p < 0.05$ , Wald-t test.

Source: NDA 20,628/20,828, Agency analysis, December 2003 (Zhou, 2003).

It is noted by this Statistical Reviewer that the significant gender difference in IDV/RTV arm as well as the treatment difference in female subjects may be due to two factors. First, at around Week 4, 37% (16/41) of female subjects in the IDV/RTV arm were dropouts or failure in virologic responses, while the non-response rates were approximately 20% in the SQV/RTV arm as well as in other two male subgroups. Second, female subjects had greater baseline plasma HIV-1 RNA levels than did male subjects: the median plasma HIV-1 RNA ( $\log_{10}$  copies/mL) were 3.5 ( $n = 122$ ) and 3.6 ( $n = 117$ ) for male subjects in SQV/RTV and IDV/RTV regimens, respectively, and 4.3 ( $n = 26$ ) and 4.6 ( $n = 40$ ) for female subjects in SQV/RTV and IDV/RTV regimens, respectively. The gender difference in baseline HIV-1 RNA levels was statistically significantly different from zero in the IDV/RTV regimen ( $p = 0.036$ ) but not in the SQV/RTV regimen ( $p > 0.05$ ) using the Wilcoxon test.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

The three PK studies in healthy volunteers were reviewed for safety. Data from BP15058 and BP15359, in which subjects received RTV-boosted SQV, were pooled by the applicant for this review. The AE profile of SQV as demonstrated in these three studies was consistent with those previously associated with SQV and/or RTV use.

In the two studies in HIV-infected patients, the safety profile of subjects who received SQV/RTV was also reviewed for safety with specific emphasis on the possible effects of SQV  $C_{min}$  and gender. It should be noted that the MaxCmin 1 study was reviewed in December 2003 for safety and efficacy. For this review process, revised datasets from this study bearing MedDRA coded AEs were re-analyzed by the Clinical and Statistical Reviewers. For both studies, Week 4 SQV  $C_{min}$  levels were provided for a subset of subjects.

In the NR15720 study, male and female subjects in the pharmacokinetic substudy had similar Week 4 SQV  $C_{min}$  levels and adverse event profiles. In the MaxCmin 1 study, the mean SQV  $C_{min}$  level for female subjects ( $n = 15$ ) was approximately 1.6 fold higher than that for male subjects ( $n = 54$ ). Moreover, in the MaxCmin 1 study, female subjects reported a higher median number of adverse events (all body systems and those involving the gastrointestinal system) and in general, experienced a shorter time to onset of such adverse events as compared to male

subjects. However, the applicant states that there was no obvious correlation between Week 4 SQV  $C_{min}$  levels and the frequency, type, and/or intensity of adverse events. With regard to laboratory parameters, in both studies, the applicant notes that there was no evidence that increased SQV  $C_{min}$  levels were correlated with organ system function, including hepatic function.

In general, these findings were confirmed by the Clinical and Statistical Reviewers. However, several limitations of the pharmacokinetic substudies, such as the relatively small number of female subjects and the heterogeneous nature of the patient population with respect to baseline factors (e.g. history of antiretroviral treatment), are noted by the Reviewers. Thus, at this time, no formal changes in the product label are requested regarding possible gender effects on SQV exposure and safety profile; the applicant will be asked to address these issues in greater detail as postmarketing commitments (Section 9.3).

#### 7.1.1 Deaths

Healthy volunteer studies: The applicant states that no deaths were reported in any of the three studies.

#### Studies in HIV-infected subjects:

NR15720: One death was reported during the course of this study. Subject #1014, a 61 year old Caucasian male who had received FTV/RTV, 3TC, and d4T for approximately seven months, died due to an acute myocardial infarction. The subject's medical history included hypothyroidism, hypertension, gastroesophageal reflux disease, obesity and insomnia. Concomitant medications included omeprazole and levothyroxine. The subject's family history was notable for two male relatives with cerebrovascular accidents. This subject initially presented with acute left-sided weakness and a facial droop. An MRI showed multiple bilateral ischemic infarcts and truncation of the right middle cerebral artery without acute hemorrhages or masses. An echocardiogram showed mild right atrial enlargement and possible diastolic left ventricular dysfunction. The subject was started on aspirin and discharged following four days of hospitalization and resolution of the presenting clinical event. However, the patient subsequently complained of nausea, dizziness, and inability to keep down antiretroviral medications. Two weeks later, the subject experienced sudden onset of chest pain and was admitted with a diagnosis of possible unstable angina. The pain resolved with nitroglycerin. A troponin level was suspicious for myocardial injury but myocardial infusion imaging showed no evidence of ischemia or infarct. On the following day, the subject was discharged to home and three days later, the subject died. No autopsy was performed. The cause of death on the death certificate was arteriosclerotic vascular disease and acute myocardial infarction. The investigator considered the cerebrovascular accident, unstable angina, and acute myocardial infarction to be unrelated to study treatment. Based on the review of this patient narrative, this Medical Officer concurs with the investigator's assessment.

MaxC<sub>min</sub> 1: The applicant notes that six deaths were reported during the course of this study. These events were reviewed by this Medical Officer and described in the December 2003

Clinical Review of NDA 20626/20828. Four deaths were reported among subjects who were randomized to receive FTV/RTV and two deaths were noted among subjects who received the comparator IDV/RTV regimen. The previous analysis of the six deaths is summarized below.

The applicant notes that three subjects died after starting the randomized treatment and one died after randomization but before being notified of the results of the randomization visit. Two subjects who died were naïve to antiretroviral treatment at the time of enrollment into the study and both had experienced AIDS-defining events (Kaposi's sarcoma (KS) and *Pneumocystis jiroveci* pneumonia (PCP), respectively) just prior to entry into the study. Both subjects were considered by the respective site investigators to be able to complete the study and that their clinical status had stabilized at the time of study entry. Patients 5 and 6 were not included in the MaxCmin 1 final study report as deaths that occurred during the study since they withdrew from the study before death.

1. Patient # 2012108, a 37 year old male who was randomized to the IDV/RTV arm, was known to have Castleman's disease (diagnosed by a lymph node biopsy a month prior to study enrollment) and history of KS of the legs. About eight weeks after commencing lamivudine, zidovudine, and IDV/RTV, the subject experienced progressive malaise, dyspnea, diarrhea and fever. The patient was started on prednisone 100 mg QD and then died due to multi-organ failure due to sepsis despite treatment with antibiotics. It is assumed by this Medical Officer that the prednisone was intended to treat the Castleman's disease.
2. Patient # 4601112, a 46 year old male with a history of PCP three weeks before the baseline visit, was started on lamivudine, zidovudine, and FTV/RTV. After about ten days of antiretroviral therapy, the patient was admitted to the hospital with sudden onset of dyspnea. "Multi-drug resistant" *S. aureus* was found in the sputum and the patient died of respiratory failure a few hours after admission.
3. Patient # 2003105, a 37 year old male with a history of PCP and "severe chronic" hepatitis C for about seven years prior to the study, had been on lamivudine, zidovudine, abacavir, and FTV/RTV for about ten months. The patient was then admitted to the hospital for a two-day history of anuria and hematemesis, as well as hypotension, confusion, jaundice, and decreased Glasgow Coma Scale. Laboratory values provided in the SAE report form showed the following: bilirubin:138 ( $\mu\text{mol/L}$ ), ESR: 52, and platelets: 17,000. The patient died two days after hospitalization due to liver failure, presumably due to hepatitis C.
4. Patient # 1501131, a 55 year old male, had been randomized to the FTV/RTV arm but was found dead at his residence before starting the study drug treatment. An autopsy revealed an old coronary thrombosis, a "weakened heart" due to an old ischemic event and a new thrombosis in the right coronary artery. The new thrombus in the right coronary artery was listed on the death certificate as the cause of death.
5. Patient #1101107, a 33 year old male, was started on lamivudine, zidovudine and IDV/RTV. About six months after starting the randomized antiretroviral therapy, the patient was diagnosed with non-Hodgkin's lymphoma. Due to gastrointestinal side effects from the chemotherapy, the patient withdrew consent from the study and then died six months after the diagnosis of lymphoma.
6. Patient #7507101, a 63 year old male, was randomized to the FTV/RTV arm and received lamivudine, stavudine, and FTV/RTV. After three months of antiretroviral therapy, the

patient underwent a right-sided hemicolectomy for colon adenocarcinoma with metastatic lesions to the liver. The patient then withdrew from the study and thereafter received only palliative care until death.

Several comments may be made regarding these deaths. First, it is plausible that at the time of hospitalization and the presumed *S. aureus* respiratory tract infection, patient #2 may have experienced immune reconstitution response (due to antiretroviral therapy) against the recent *Pneumocystis* infection. Second, it is unclear whether the “multidrug resistant” *S. aureus* from patient #2 corresponds to *S. aureus* that is resistant to methicillin or to other antibacterial agents. Third, it is possible that the administration of prednisone to patient #1 (presumably to treat Castleman’s disease) may have predisposed this patient to infections that led to his clinical decompensation with physiological changes consistent with sepsis. Fourth, given the nature and severity of the underlying medical conditions, patient #1 should have been excluded from the study and classified as a protocol violation. Fifth, given the underlying hepatitis C infection, the possibility that study medications played a role in hepatic decompensation and death of patient #3 cannot be excluded. Aside from patient #3, there appears to be no evidence that the study-related antiretroviral therapy of other five patients may have contributed to the deaths.

#### 7.1.2 Other Serious Adverse Events

Healthy volunteer studies: As noted by the applicant and confirmed by this Medical Officer, no serious adverse events (SAEs) were reported in any of the three studies.

#### Studies in HIV-infected subjects:

NR15720: The applicant reports that seven subjects (8.6%) who received SQV/RTV reported at least one SAE. The SAEs that were reported during the study included: neutropenia, idiopathic thrombocytopenic purpura, gastric erosions, incisional hernia, scrotal infection, back pain, urinary incontinence, cerebrovascular accident, and unstable angina. The last two SAEs were reported in one subject who died from a myocardial infarction (see Section 7.1.1, above). According to the applicant, none of the SAEs were deemed to be related to the study medications by the investigators. Upon review of the SAE narratives, this Medical Officer concurs with the assessment by the investigators. It is noted by this Medical Officer that one SAE (neutropenia in subject 1034) may have been related to zidovudine that was being administered concomitantly with SQV/RTV.

MaxCmin 1: The applicant states that 35 SAEs were reported by 23 subjects who were randomized to the SQV/RTV arm. The most frequently reported SAEs were pneumonia (5 events), anemia (3 events) and gastrointestinal events such as abdominal pain (4 events), nausea (3 events), and vomiting (2 events). One subject with a history of epilepsy was hospitalized following grand mal seizures which were deemed possibly related to RTV and remotely/unlikely to be related to SQV according to the investigator. Three other subjects had SAEs (dizziness/vision disorder, anemia, and abdominal pain/nausea/vomiting) which were all considered to be at least remotely related to study treatment by the investigator. The narratives for these four cases have been reviewed by this Medical Officer, who concurs with the

investigators' assessments. It should be noted that this Medical Officer has previously reviewed all SAEs in the MaxCmin 1 study (Murata, 2003).

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

##### Healthy volunteer studies:

In Study BP17653, the applicant states that no subjects withdrew prematurely from the study.

In Study BP17358, the applicant notes that one subject withdrew during the RTV run-in period and prior to receiving the first dose of SQV. Subject 0011 experienced mild diarrhea and moderate vomiting on day 9 and withdrew from the study on the same day. The events resolved without sequelae and the events were judged by the investigator to be remotely related to RTV.

In Study BP17359, the applicant states that five subjects withdrew prematurely from the study due to AEs. Four subjects withdrew during the RTV run-in phase before the first dose of SQV. The AEs experienced by these four were: severe vomiting/moderate abdominal pain/moderate diarrhea (all probably related to RTV); severe headache/mild dizziness/mild nausea (possibly/probably related to RTV); moderate wound infection following right ankle laceration (unrelated to RTV); and moderate dry throat/mild headache/moderate rhinorrhea (remotely related to RTV). One subject experienced a mild headache (possibly related to RTV), and following the first dose of INV HGC, reported moderate nausea and severe vomiting (deemed possibly related to RTV and INV HGC) before withdrawing from the study. Except for the ankle laceration (unresolved at the time of database closure), these events resolved without sequelae.

This Medical Officer has reviewed the case summaries for all of these events and agrees with the assessments of the investigators.

##### Studies in HIV-infected subjects:

NR15720: The applicant reports that 12 subjects who received SQV/RTV experienced AEs that led to withdrawal from the study. Of these, eight subjects discontinued study treatment due to nausea and/or vomiting that were deemed to be probably related to study drug. Other treatment-discontinuing AEs included retching, anxiety, dizziness, nocturia, abdominal distension, decreased appetite, sickness, chest pain, and fatigue; almost all of these events were deemed to be at least possibly related to study treatment. All events were mild or moderate in severity except for two incidences of severe nausea. This Medical Officer has reviewed the case summaries for all of these events and agrees with the assessments of the investigators.

MaxCmin 1: The overall profile of dropouts from this study has previously been analyzed by the applicant and reviewed by this Medical Officer (Murata, 2003). The applicant reports in this

NDA that 22 subjects receiving FTV/RTV withdrew from the study treatment due to AEs. The most common AEs for such withdrawals were gastrointestinal in nature, including vomiting (five subjects) and diarrhea (two subjects). Of study withdrawals due to gastrointestinal AEs, seven were deemed at least possibly related to treatment; one was due to a Grade 3 event (vomiting) while others experienced Grade 1 or 2 events.

In all, 14 subjects (12 males, 2 females) who were randomized to receive FTV/RTV experienced a dose adjustment, interruption, or switching of SQV formulation to INV HGC. It is noted by this Medical Officer that Week 4 SQV  $C_{min}$  levels are available for five of these patients. Four out of five were males (#2004102: 3065 ng/mL, #2012014: 712 ng/mL, #3002101: 384 ng/mL, and #3002102: 1562 ng/mL) and one was female (#1000108: 2372 ng/mL). In the opinion of this Medical Officer, given the limited sample size, no clinically relevant conclusions may be drawn from the SQV PK values and their relationship to the AEs in these five subjects.

#### 7.1.3.2 Adverse events associated with dropouts

Please see Section 7.1.3.1.

#### 7.1.3.3 Other significant adverse events

For all five clinical studies in this NDA, analysis of laboratory results are described in Section 7.1.7.

#### 7.1.4 Other Search Strategies

Healthy Volunteer Studies: Please see the Appendix of this review for the summaries of the three PK studies. The AEs are described in Section 7.1.5.

Studies in HIV-Infected Subjects: The applicant presents data from PK substudies within the NR15720 and MaxCmin 1 studies. These analyses to explore the effects of gender and SQV exposure on the AE profile of study participants are reviewed in Section 7.1.12.

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

For previously approved formulations of SQV (FTV and INV HGC), clinical experience and reports in medical literature have shown that the most commonly reported SQV-associated AEs are gastrointestinal in nature. In some patients, the excipient Capmul in FTV has been associated with an increased incidence of gastrointestinal AEs.

For the clinical development of the new SQV formulation as INV 500 mg FCT, no new efficacy studies were performed in HIV-infected patients and limited safety data from healthy volunteers are provided in this NDA. As noted by the applicant and as agreed upon in principle by this

Medical Officer, the AE profile of INV FCT is likely to be similar to those of INV HGC and FTV, with the exception that the FCT does not contain the excipient Capmul.

With regard to applicant's analysis of AEs, four points are noted by this Medical Officer: 1) the AEs for studies BP17058 and BP17359 were pooled by the applicant for analysis; 2) the AEs noted during the MaxCmin 1 study were initially coded using the WHO ICD 10 coding and were not initially subjected to a thorough quality check (this was previously noted by this Medical Officer; Murata, 2003); 3) for this NDA, the applicant has re-submitted MaxCmin 1 AEs that have been re-coded using MedDRA; and 4) the review of the safety profile of the once-daily SQV/RTV regimen in NR15720 is strictly for gender and SQV exposure substudies since the applicant has not formally submitted this dosing regimen for regulatory approval by the Agency.

#### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

In the context of points noted in Section 7.1.5.1, this Medical Officer believes that the adverse event categorizations that are provided in this NDA are appropriate.

#### 7.1.5.3 Incidence of common adverse events

##### Healthy volunteer studies:

RTV-Unboosted Study BP17653: Please refer to the Appendix of this review for the safety summary of this study. In the opinion of this Medical Officer, the clinical significance of the safety profile of INV FCT as shown in this study is unclear due to the following: 1) the limited size and scope of the study; and 2) dosing of INV FCT in healthy volunteers and without concomitant RTV administration.

RTV-Boosted Studies BP17058 and BP17359 (Pooled Dataset): The applicant states that in these studies, the single doses of INV FCT/RTV and INV HGC/RTV were relatively well tolerated. In this pooled patient population, 72 subjects (60%) reported 144 AEs during the RTV 100 mg BID run-in period, 25 subjects (22.1%) reported 35 AEs during the INV HGC/RTV treatment periods, and 33 subjects (29.7%) reported 40 AEs during the INV FCT/RTV periods. The AEs are summarized on the following Table 3:

Table 3. Summary of All AEs ( $\geq 2\%$  in Any Group) during Studies BP17058 and BP17359.

Body System/AE	All Periods RTV 100 mg BID N = 120		All Periods INV HGC 1000 mg + RTV 100 mg BID N = 113		All Periods INV FCT 1000 mg + RTV 100 mg BID N = 111	
	#	%	#	%	#	%
<b>All Body Systems</b>						
Total # with $\geq 1$ AE	72	60.0	25	22.1	33	29.7
Total # of AEs	144		35		40	
<b>Gastrointestinal Disorders</b>						
Total # with $\geq 1$ AE	31	25.8	13	11.5	18	16.2
Diarrhea	15	12.5	6	5.3	7	6.3
Nausea	8	6.7	3	2.7	3	2.7

Abdominal Pain	3	2.5	2	1.8	3	2.7
Loose Stools	1	0.8	3	2.7	3	2.7
Watery Stools	2	1.7	1	0.9	3	2.7
Flatulence	5	4.2	-	-	-	-
Total # AEs	46		18		20	
<b>Nervous System Disorders</b>						
Total # with $\geq 1$ AE	34	28.3	12	10.6	16	14.4
Headache	30	25.0	11	9.7	15	13.5
Dizziness	6	5.0	-	-	-	-
Total # AEs	39		12		16	
<b>General Disorders and Administration Site Conditions</b>						
Total # with $\geq 1$ AE	16	13.3	3	2.7	1	0.9
Fatigue	8	6.7	3	2.7	1	0.9
Lethargy	3	2.5	1	0.9	-	-
Total # AEs	21		3		1	
<b>Respiratory Disorders</b>						
Total # with $\geq 1$ AE	10	8.3	1	0.9	1	0.9
Pharyngolaryngeal Pain	4	3.3	-	-	-	-
Total # AEs	12		1		1	
<b>Infections and Infestations</b>						
Total # with $\geq 1$ AE	9	7.5	1	0.9	1	0.9
Nasopharyngitis	5	4.2	-	-	-	-
Total # AEs	9		1		1	
<b>Musculoskeletal and Connective Tissue Disorders</b>						
Total # with $\geq 1$ AE	6	5.0	-	-	-	-
Total # AEs	6		-		-	
<b>Skin Disorders</b>						
Total # with $\geq 1$ AE	5	4.2	-	-	-	-
Total # AEs	6		-		-	

Source: Adapted from NDA 21,785, Module 2, Vol. 1, pp. 26-28.

The applicant notes that the most frequently reported AEs were headaches reported by 30 subjects (25%) during the RTV run-in period, 11 subjects (9.7%) during the INV HGC/RTV periods, and 15 subjects (13.5%) in the INV FCT/RTV periods.

According to the applicant, the body system associated with the most AEs in the two studies was the gastrointestinal system. A total of 31 subjects (25.8%) reported  $\geq 1$  gastrointestinal AE during the RTV run-in period as compared to 13 subjects (11.5%) during the INV HGC/RTV periods and 18 subjects (16.2%) during the INV FCT/RTV periods. Of the gastrointestinal AEs, diarrhea was the most frequently reported AE that was noted in 15 subjects (12.5%) during the RTV run-in periods, six subjects (5.3%) during the INV HGC/RTV periods, and seven subjects (6.3%) during the INV FCT/RTV treatment periods.

The applicant notes that the majority of AEs reported during the study period were deemed by the investigators to be possibly related to treatment with RTV, INV FCT, or INV HGC. Within the pooled study population, only three subjects experienced AEs (severe headache, mild diarrhea, and moderate nausea/severe vomiting/moderate abdominal pain/moderate diarrhea) which were deemed to be probably related to study treatment.

According to the study investigators, most AEs reported during the study drug dosing periods were considered mild in intensity. During the INV HGC/RTV dosing periods, two subjects reported severe AEs (headache and vomiting). No severe AEs were reported during the INV FCT/RTV treatment periods. Three severe AEs (headache x 2 and vomiting) were reported by three subjects during the RTV run-in periods.

The applicant also analyzed the temporal association between SQV administration and the occurrence of AEs recorded during the study. To this end, the applicant provides a summary listing of all AEs which occurred with 48 hours of administration of scheduled doses of INV HGC/RTV or INV FCT/RTV. Headache was the only AE which appeared to show any temporal relationship to INV administration. A total of 10 subjects (18.0% of subjects randomized to receive INV FCT/RTV as the first phase of INV dosing) reported headaches within 48 hours following dosing of INV. During the remaining dosing phases, headache was reported only three times by subjects who previously reported the event. In contrast, among subjects who received INV HGC/RTV as the first phase of INV dosing, no differences were identified in the occurrence of headache between this phase and the following three phases.

These findings have been confirmed by this Medical Officer following the review of data tables and line listings. The clinical significance of the possible temporal relationship between SQV/RTV dosing and headaches is unclear, especially given the small size of the pooled study population of healthy volunteers. In addition, although the dosing intervals for INV/RTV were 72 hours, the applicant provided AE analysis for 48 hours following dosing. In the opinion of this Medical Officer, this minor difference in the AE reporting window periods is not expected to significantly alter the safety profile of INV/RTV regimens as used in these studies (also see Section 7.1.5.6).

Studies in HIV-infected subjects:

NR15720: According to the applicant, AEs were reported by approximately 98% of subjects (N = 81 in the safety population) receiving SQV/RTV during the study. The most frequently reported AEs were gastrointestinal in nature and were noted by 82% of patients. Among the AEs reported by ≥ 10% of patients, nausea (45.7%), diarrhea (33.3%), vomiting (22.2%), abdominal pain (22.0%) and decreased appetite (14.8%) were most frequently reported. A summary of all AEs reported with a frequency ≥ 5% during the study among subjects who received SQV/RTV is shown in Table 4.

Table 4. Study NR15720: Summary of AEs by Body System Recorded at a Frequency of ≥ 5% in the SQV/RTV Arm During the Study.

Body System/AE	# (N = 81)	%
<b>Gastrointestinal Disorders</b>		
Abdominal Distension	6	7
Abdominal Pain NOS	11	14
Abdominal Pain Upper	7	9
Constipation	6	7
Diarrhea NOS	27	33
Dyspepsia	4	5

Clinical/Statistical Review

Yoshihiko Murata, M.D., Ph.D., Susan Zhou, Ph.D.

NDA 21785, N-000

INVIRASE® (saquinavir mesylate) 500 mg film-coated tablets

Flatulence	6	7
Nausea	37	46
Vomiting NOS	18	22
<b>Blood &amp; Lymphatic Disorders</b>		
Lymphadenopathy	4	5
<b>Metabolic &amp; Nutritional Disorders</b>		
Appetite Decreased	12	15
Weight Decreased	4	5
<b>General Disorders</b>		
Chest pain NOS	5	6
Dizziness	7	9
Fatigue	17	21
Pain in Limb	4	5
Pyrexia	8	10
<b>Infections &amp; Infestations</b>		
Bronchitis NOS	6	7
Herpes Zoster	4	5
Nasopharyngitis	4	5
URI NOS	16	20
<b>Musculoskeletal Disorders</b>		
Back Pain	7	9
<b>Neurological Disorders</b>		
Headache NOS	13	16
Hypoaesthesia	7	9
Insomnia	5	6
Paresthesia	5	6
Peripheral Neuropathy NOS	6	7
<b>Psychiatric Disorders</b>		
Depression NOS	9	11
<b>Respiratory Disorders</b>		
Cough	7	9
Sinus Congestion	6	7
<b>Skin &amp; Subcutaneous Tissue Disorders</b>		
Dermatitis NOS	8	10
Night Sweats	5	6
Pruritis	5	6
Skin Lesion NOS	6	7
<b>Vascular Disorders</b>		
Hypertension NOS	3	3

Source: Adapted from NDA 21.785, Module 2, Vol. 1, p. 30.

This Medical Officer has confirmed the numbers shown in Table 4. Minor differences between the applicant's analysis and that of this Medical Officer were noted but were not considered to significantly alter the conclusions reached by the applicant. It is also noted by this Medical Officer that the AE profile of the SQV/RTV regimen used in study NR15720 is consistent with that reported during the clinical experience with SQV.

This Medical Officer extended the applicant's analysis by performing exploratory studies on the possible effects of gender on the AE profile of SQV/RTV as used in this study. Based on the data provided by the applicant (Module 5, Vol. 14, p. 88 and p. 90), there were 56 males and 25 females in the safety population. It is noted by this Medical Officer that in general, the types of AEs reported by male subjects who received SQV/RTV were not significantly different from those noted by female participants. In both gender groups, the most commonly reported AEs

were gastrointestinal in nature (Table 5). It is noted by this Medical Officer that as compared to female subjects, twice as many male subjects experienced diarrhea. Otherwise, no significant differences were noted with regard to the number of subjects (male vs. female) that reported gastrointestinal AEs. It should be noted that for the same AE with multiple occurrences, each patient was counted once. Thus, this analysis is not intended to show the frequency of reporting for each gastrointestinal AE. The applicant performed additional AE analysis by gender for the PK substudy population (reviewed in Section 7.1.12).

Table 5. Study NR15720: Exploratory Gender Analysis of Gastrointestinal AEs Reported by Subjects in the SQV/RTV Safety Population.

Body System/AE	Female Patients N = 25		Male Patients N = 56	
	# of Patients	%	# of Patients	%
<b>Gastrointestinal Disorders</b>				
Diarrhea NOS	5	20	22	39
Nausea	10	40	27	48
Vomiting NOS	7	28	11	20
Abdominal Pain NOS	3	12	8	14
Flatulence	1	4	5	9
Abdominal Distension	2	8	4	7
Abdominal Pain Upper	3	12	4	7
Constipation	3	12	3	5

Note: For the same AE with multiple occurrences, each patient is counted once.

Source: Agency analysis, NDA 21,785 datasets.

For the safety population that received SQV/RTV in study NR15720, the applicant's summary of AEs, including relationship to treatment and intensity, is shown in Table 6. The majority of AEs were graded as mild or moderate. One patient who subsequently died (see Section 7.1.1, above) experienced myocardial infarction and cerebrovascular accident, both of which were graded as life-threatening.

Table 6. Study NR15720: Overall Summary of AEs in the Safety Population of Arm A (SQV/RTV).

<b>Total AEs:</b>				
Total # of patients with at least one AE	79 (97.5%)			
Total # of AEs	575			
<b>Relationship to Study Treatment*</b>	Unrelated	Remotely	Possibly	Probably
Total # with at least one AE	65 (80.2%)	0	48 (59.3%)	33 (40.7%)
Total # of AEs	356	0	167	52
<b>Intensity**</b>	Mild	Moderate	Severe	Life-threatening
Total # with at least one AE	78 (96.3%)	48 (59.3%)	14 (17.3%)	1 (1.2%)
Total # of AEs	374	176	23	2

\*: For the same AE with multiple occurrences, each patient is counted once with the highest relationship to treatment.

\*\* : For the same AE with multiple occurrences, each patient is counted once with the highest intensity. It is noted by this Medical Officer that due to database formats, these numbers regarding intensity of AEs were not independently confirmed; this is not expected to significantly alter the interpretation of these results.

Source: Adapted from NDA 21,785, Module 5, Vol. 14, pp. 72-3.

The applicant also provides the following table for the AEs reported within the SQV PK substudy population (N = 60) during the study:

Table 7. Study NR15720: Summary of AEs by Body System Recorded at a Frequency of  $\geq 5\%$  Within the SQV PK Substudy Population.

Body System/AE	N = 60 #	%
<b>All Body Systems</b>		
Patients having $\geq 1$ AE	58	97
Total # of AEs	473	
<b>Gastrointestinal Disorders</b>		
Patients having $\geq 1$ AE	49	82
Nausea	27	45
Diarrhea NOS	22	37
Vomiting NOS	12	20
Abdominal Pain NOS	10	17
Flatulence	6	10
Abdominal Pain Upper	5	8
Esophageal Reflux	4	7
Abdominal Distension	3	5
Constipation	3	5
Dyspepsia	3	5
Dysphagia	3	5
Total # AEs	121	
<b>Infections and Infestations</b>		
Patients having $\geq 1$ AE	37	62
URI	14	23
Bronchitis NOS	6	10
Herpes Zoster	4	7
Influenza	4	7
Nasopharyngitis	4	7
Venereal Warts	4	7
Sinusitis NOS	3	5
Tinea Pedis	3	5
UTI NOS	3	5
Total # AEs	84	
<b>General Disorders</b>		
Patients having $\geq 1$ AE	30	50
Fatigue	14	23
Dizziness	5	8
Pyrexia	5	8
Chest Pain NOS	4	7
Pain in Limb	4	7
Total # AEs	42	
<b>Neurological Disorders</b>		
Patients having $\geq 1$ AE	24	40
Headache NOS	9	15
Peripheral Neuropathy NOS	6	10
Hypoesthesia	5	8
Parasthesia	5	8
Insomnia	4	7
Total # AEs	44	
<b>Respiratory Disorders</b>		
Patients having $\geq 1$ AE	24	40
Cough	6	10
Sinus Congestion	4	7

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Sore Throat NOS	4	7
Total # AEs	32	
<b>Skin Disorders</b>		
Patients having $\geq 1$ AE	22	37
Dermatitis NOS	8	13
Skin Lesion NOS	6	10
Night Sweats	5	8
Pruritis	5	8
Total # AEs	39	
<b>Disorders of Metabolism</b>		
Patients having $\geq 1$ AE	16	27
Appetite Decreased	7	12
Cachexia	3	5
Weight Decreased	3	5
Weight Increased	3	5
Total # AEs	18	
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Patients having $\geq 1$ AE	12	20
Back Pain	7	12
Myalgia	3	5
Total # AEs	15	
<b>Psychiatric Disorders</b>		
Patients having $\geq 1$ AE	12	20
Depression NOS	8	13
Total # AEs	21	
<b>Cardiac Disorders</b>		
Patients having $\geq 1$ AE	7	12
Total # AEs	9	
<b>Disorders of the Eye</b>		
Patients having $\geq 1$ AE	7	12
Conjunctivitis NOS	4	7
Total # AEs	7	
<b>Injury and Poisoning</b>		
Patients having $\geq 1$ AE	7	12
Total # AEs	8	
<b>Renal Disorders</b>		
Patients having $\geq 1$ AE	7	12
Nocturia	3	5
Total # AEs	8	
<b>Disorders of Blood and Lymphatics</b>		
Patients having $\geq 1$ AE	6	10
Total # AEs	6	
<b>Disorders of the Reproductive System</b>		
Patients having $\geq 1$ AE	6	10
Impotence	4	7
Total # AEs	6	
<b>Benign and Malignant Neoplasms</b>		
Patients having $\geq 1$ AE	4	7
Total # AEs	4	
<b>Vascular Disorders</b>		
Patients having $\geq 1$ AE	3	5
Total # AEs	3	

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Source: Adapted from NDA 21,785, Module 2, Vol. 1, pp. 83-87.

The numbers in Table 7 were confirmed by this Medical Officer and only minor differences between the applicant's analysis and the Agency's analysis were noted. Again, the AE profile of

the SQV/RTV PK substudy population is consistent with that noted with the clinical experience with SQV. In addition, the AE profile of the patients in the PK substudy is similar to that of the entire SQV/RTV population as shown in Table 4.

This Medical Officer has also examined the gender effects of AEs reported by subjects in the PK substudy (42 males, 18 females). As was previously noted for the entire SQV/RTV safety population, the most common AEs were gastrointestinal in nature. Otherwise, in the opinion of this Medical Officer, there were no significant differences in the types of AEs reported by males and by females; many AEs were reported by one subject in each gender. Please refer to Section 7.1.12 for the review of the applicant's additional AE analysis by gender for the PK substudy population.

MaxCmin 1: The safety profile and AEs associated with the FTV/RTV BID regimen in the MaxCmin 1 study has previously been reviewed (Murata, 2003). The current INV HGC label bears the safety analysis from the MaxCmin 1 study.

As summarized in this NDA, the applicant reports that at 48 weeks, 73% of the 148 subjects who started treatment with SQV/RTV were still taking the study drug treatment. The mean duration of exposure to study drug medication for 148 subjects in the SQV/RTV arm was 41 weeks.

The applicant states that a total of 119/148 (80.4%) patients that received SQV/RTV with other antiretroviral agents reported at least one AE during the study. The most frequently reported AEs were gastrointestinal in nature (73/148 (49.3%)). Diarrhea (reported by 21.0% of patients), nausea (18.2%), vomiting (12.2%), abdominal pain (10.8%), and fatigue (12.2%) were the most frequently reported AEs that were reported by at least 10% of the patients.

In this NDA, the applicant has provided revised AE datasets that contain MedDRA-coded AEs. In addition, the applicant provides tables and analyses of AEs based on gender as well as a comparison of the AE profile of the PK substudy population with that of the entire population that received SQV/RTV.

As shown in Table 8, the AE profiles of female and male subjects in the SQV/RTV arm of the MaxCmin 1 study are compared to that of the entire SQV/RTV population. In most of the AE categories, it is noted by this Medical Officer that more females than males reported AEs. With respect to this observation, the applicant presents a detailed analysis of gastrointestinal AEs (reviewed in Section 7.1.5.6). This Medical Officer notes the following: 1) there are significantly fewer females (n = 26) subjects as compared to males (n = 122) in this study arm; 2) no previously unidentified SQV-associated AEs are obvious in the safety analysis by gender; and 3) historical data from early clinical/registrational studies for SQV predominantly involved male subjects and thus may not provide gender-matched comparative data. As these points are taken into consideration with the Statistical Reviewer's safety analysis by gender, it is the opinion of both Clinical and Statistical Reviewers that the effects of gender and SQV C<sub>min</sub> levels on the safety profile of SQV be further studied as postmarketing commitments (see Section 9.3.2).

Table 8. Summary of All AEs ≥ 5% of Subjects in Any Study Arm during Study Treatment plus 30 days: All Patients who Received SQV/RTV in the MaxCmin 1 Study.

Body System/AE	All patients N = 148		Female Patients N = 26		Male Patients N = 122	
	#	%	#	%	#	%
<b>All Body Systems</b>						
Patients having ≥ 1 AE	119	80	22	85	97	80
Total # of AEs	445		109		336	
<b>Gastrointestinal Disorders</b>						
Patients having ≥ 1 AE	73	49	15	58	58	48
Diarrhea NOS	31	21	5	19	26	21
Nausea	27	18	7	27	20	16
Vomiting NOS	18	12	7	27	11	9
Abdominal Pain NOS	16	11	5	19	11	9
Flatulence	11	7	2	8	9	7
Constipation	5	3	2	8	3	2
Total # AEs	142		29		113	
<b>General Disorders</b>						
Patients having ≥ 1 AE	38	26	11	42	27	22
Fatigue	18	12	5	19	13	11
Pyrexia	10	7	2	8	8	7
Influenza like illness	6	4	4	15	2	2
Total # AEs	45		13		32	
<b>Infections and Infestations</b>						
Patients having ≥ 1 AE	37	25	9	35	28	23
Sinusitis NOS	4	3	2	8	2	2
Total # AEs	47		11		36	
<b>Skin and Subcutaneous tissue disorders</b>						
Patients having ≥ 1 AE	29	20	8	31	21	17
Eczema NOS	7	5	1	4	6	5
Rash NOS	7	5	1	4	6	5
Dry skin	6	4	2	8	4	3
Pruritis NOS	6	4	0	0	6	5
Total # AEs	37		9		28	
<b>Laboratory Investigations</b>						
Patients having ≥ 1 AE	27	18	8	31	19	16
ALT Increased	5	3	2	8	3	2
Total # AEs	49		14		35	
<b>Nervous system disorders</b>						
Patients having ≥ 1 AE	23	16	8	31	15	12
Dizziness	4	3	3	12	1	1
Total # AEs	23		8		15	
<b>Blood and Lymphatic system disorders</b>						
Patients having ≥ 1 AE	15	10	3	12	12	10
Anemia NOS	9	6	2	8	7	6
Total # AEs	15		3		12	
<b>Musculoskeletal and Connective Tissue disorders</b>						
Patients having ≥ 1 AE	12	8	5	19	7	6
Back Pain	2	1	2	8	0	0
Total # AEs	14		6		8	
<b>Respiratory Disorders</b>						

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Patients having $\geq 1$ AE	12	8	1	4	11	9
Total # AEs	13		1		12	
<b>Metabolism and nutrition disorders</b>						
Patients having $\geq 1$ AE	11	7	5	19	6	5
Anorexia	3	2	2	8	1	1
Appetite increased NOS	2	1	2	8	1	1
Total # AEs	12		5		7	
<b>Congenital, Familial, and Genetic Disorders</b>						
Patients having $\geq 1$ AE	7	5	2	8	5	4
Lipodystrophy congenital	7	5	2	8	5	4
Total # AEs	7		2		5	
<b>Psychiatric Disorders</b>						
Patients having $\geq 1$ AE	7	5	1	4	6	5
Total # AEs	9		1		8	
<b>Renal and Urinary Disorders</b>						
Patients having $\geq 1$ AE	5	3	0	0	5	4
Total # AEs	6		0		6	

Source: Adapted from NDA 21,785, Module 2, Vol. 1, pp. 88-98.

In Table 9, the applicant presents a summary of AEs that occurred in the subjects enrolled in the PK substudy. Using the revised and recoded AE datasets for the MaxCmin 1 study, this Medical Officer has confirmed the numbers shown in Tables 8 and 9; minor differences between the Agency's analysis of the AEs and that of the applicant are unlikely to be of clinical significance.

Table 9. Summary of AEs during Study Treatment  $\geq 5\%$  of Subjects with SQV Concentration Measured at Week 4: MaxCmin 1 Study.

Body System/AE	N = 69 #	%
<b>All Body Systems</b>		
Patients having $\geq 1$ AE	54	78
Total # of AEs	229	
<b>Gastrointestinal Disorders</b>		
Patients having $\geq 1$ AE	35	51
Diarrhea NOS	18	26
Nausea	11	16
Abdominal pain NOS	10	14
Flatulence	8	12
Vomiting NOS	7	10
Abdominal pain upper	4	6
Total # AEs	74	
<b>General Disorders</b>		
Patients having $\geq 1$ AE	19	28
Fatigue	7	10
Pyrexia	6	9
Influenza like illness	5	7
Total # AEs	24	
<b>Infections and Infestations</b>		
Patients having $\geq 1$ AE	17	25
Pneumonia NOS	4	6
Total # AEs	22	

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<b>Skin and Subcutaneous Tissue Disorders</b>		
Patients having $\geq 1$ AE	14	20
Eczema NOS	4	6
Total # AEs	19	
<b>Laboratory Investigations</b>		
Patients having $\geq 1$ AE	15	22
ALT Increased	5	3
Total # AEs	27	
<b>Nervous System Disorders</b>		
Patients having $\geq 1$ AE	16	23
Headache NOS	5	7
Dysgeusia	4	6
Peripheral Neuropathy NOS	4	6
Total # AEs	16	
<b>Renal Disorders</b>		
Patients having $\geq 1$ AE	5	7
Total # AEs	6	
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Patients having $\geq 1$ AE	6	9
Total # AEs	7	
<b>Respiratory Disorders</b>		
Patients having $\geq 1$ AE	5	7
Total # AEs	5	
<b>Metabolism and Nutrition Disorders</b>		
Patients having $\geq 1$ AE	9	13
Total # AEs	9	

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Source: Adapted from NDA 21,785, Module 2, Vol. 1, pp. 99-101.

It is also noted by this Medical Officer that: 1) the distribution of the types of AEs reported in the PK subgroup is similar to that for the entire SQV/RTV study arm; and 2) most of the AEs occurred in  $< 5\%$  of participants in the PK substudy. Lastly, this Medical Officer performed a preliminary analysis of AEs by gender within the PK substudy population and found that most of the AEs were reported by only one subject in one or both gender groups. Further analysis of gender effects on the AE profile of the substudy population has been performed by the applicant and reviewed by the Clinical and Statistical Reviewers (Section 7.1.5.6).

The applicant also notes that the majority of AEs reported during the study were mild or moderate in intensity. According to the applicant, 35 patients (23.6%) who received SQV/RTV reported 71 Grade 3/4 AEs (Table 10). The most frequently affected body system was the gastrointestinal system. These Grade 3/4 AEs have previously been reviewed by this Medical Officer (Murata, 2003).

Table 10. MaxCmin 1: Number and Percentage of AEs of Grade 3/4 by Organ System.

Body System/AE	# (N = 148)	%
All Body Systems (N = 71)		
Nervous system	4	5.6
Cardiovascular system	1	1.4
Pulmonary system	3	4.2

Renal system	2	2.8
Gastrointestinal system	17	23.9
Skin	5	7.0
Fatigue/fever	4	5.6
Laboratory	24	33.8
Hepatic	1	1.4
Musculoskeletal	1	1.4
Other	9	12.7

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Source: NDA 21,785 Module 2, Vol. 1, p. 32.

This Medical Officer has also extended the safety analysis to examine Grade 3 and 4 AEs by gender within the PK substudy population. A total of 13 subjects reported 29 Grade 3/4 AEs within the PK substudy, with three female subjects reporting six events and ten male subjects reporting 23 events. No obvious trends in the types of Grade 3/4 AEs with respect to gender were noted.

#### 7.1.5.4 Common adverse event tables

Please refer to the previous section as well as the Appendix for the common AE tables presented in this NDA.

#### 7.1.5.5 Identifying common and drug-related adverse events

Please refer to section 7.1.5.3 as well as the Appendix for the discussion of study drug-related AEs in the five studies of this NDA.

#### 7.1.5.6 Additional analyses and explorations

Based on literature reports of gender effects on SQV exposure, the applicant has focused additional safety analysis on the clinical AEs that are gastrointestinal in nature (diarrhea, nausea, vomiting, and abdominal pain) and laboratory AEs that are hepatic in nature (including AST, ALT, and bilirubin) that may be correlated with SQV plasma concentrations. To this end, the applicant has extended the safety analysis as follows:

1. Subanalyses of studies BP17058 and BP17359 in healthy volunteers to determine whether or not there was any evidence of a difference in the AE profile with respect to the treatment group (INV HGC vs. INV FCT formulations) and by gender. Specifically, time-to-GI AEs analysis was performed in the pooled safety dataset of these two studies.
2. Subanalyses of studies NR15720 and MaxCmin 1 in HIV-infected subjects to determine the possible effects of gender and SQV  $C_{min}$  values on the AE profile of study participants.
3. Assessment of the correlation between the hepatic function tests and SQV concentrations among HIV-infected subjects in MaxCmin 1 and NR15720.

The first two analyses are reviewed in this section, whereas the analyses of hepatic function tests are reviewed in section 7.1.7.4.

Healthy volunteer studies: Time-to GI AEs: The applicant analyzed time-to-onset of selected GI AEs (abdominal pain, diarrhea, nausea, and vomiting) in the healthy volunteer studies (pooled data from studies BP17058/BP17359). The applicant presents a Kaplan-Meier analysis and states that subjects experienced such GI AEs more rapidly following the administration of INV FCT than following the administration of INV HGC. The applicant also notes that the overall proportion of subjects with these GI AEs was small (8% vs. 12%) and was not accompanied by a clinically significant change in the severity of these AEs.

The Kaplan-Meier and supporting analyses have been reviewed by the Medical Officer, who notes the following: 1) the GI AE list that was used by the applicant did not include GI AEs aside from those coded as abdominal pain, diarrhea, nausea, and vomiting; 2) the time window of AE reporting was up to 48 hours post-dose, whereas INV (as HGC or FCT) was administered every 72 hours and thus AEs that occurred between 48 and 72 hours post-dose may not have been included in the applicant's analysis; and 3) the clinical relevance of time-to-GI AE is unclear in the context of PK studies involving limited SQV dosing in healthy volunteers.

To extend the safety analysis for this Clin/Stats Review, this Medical Officer performed a re-analysis of the data using the following parameters: 1) the definition of GI AEs were expanded to include abdominal pain (NOS, lower, or upper), diarrhea, loose stools, nausea, watery stools, and vomiting; 2) the time window for AE reporting following each dose was extended to 72 hours. No Kaplan-Meier analysis was performed, but the GI AEs were identified by treatment group. Overall, no significant differences were noted between the applicant's analyses and those performed as described above by this Medical Officer.

It should be noted that in this pooled analysis, all but two AEs were reported among male subjects. In the context of these limited dosing, crossover studies in healthy volunteers, the clinical significance of this disparate distribution of GI AEs and gender is unclear, especially since there were only seven female subjects in the pooled study population.

#### Clinical Studies in HIV-Infected Patients:

NR15720: The following two paragraphs as well as Figure 2 and Table 11 describe the Statistical Reviewer's review of the applicant's data. In the SQV/RTV safety population ( $n = 81$ ), 60 subjects (74%) had Week 4 SQV  $C_{\min}$  plasma concentrations entered in the applicant's datasets. The safety population included subjects who had at least one dose of study drug and had at least one post-baseline safety evaluation (NDA 21,785, Module 5, Vol. 14, Section 2.10.3), and the time window for the PK data analysis was defined as Week 4  $\pm$  2 weeks from the baseline visit.

The Week 4 SQV  $C_{\min}$  distribution for the entire PK substudy population and identified by gender are provided in Table 11. One female and two male subjects had significantly elevated SQV  $C_{\min}$  levels  $> 2400$  ng/mL. Female subjects had slightly higher mean and median SQV  $C_{\min}$  than male subjects but the differences were not statistically significant by the Kruskal-Wallis Test ( $p = 0.6984$ ). Figure 2 displays frequencies of SQV  $C_{\min}$  by gender.

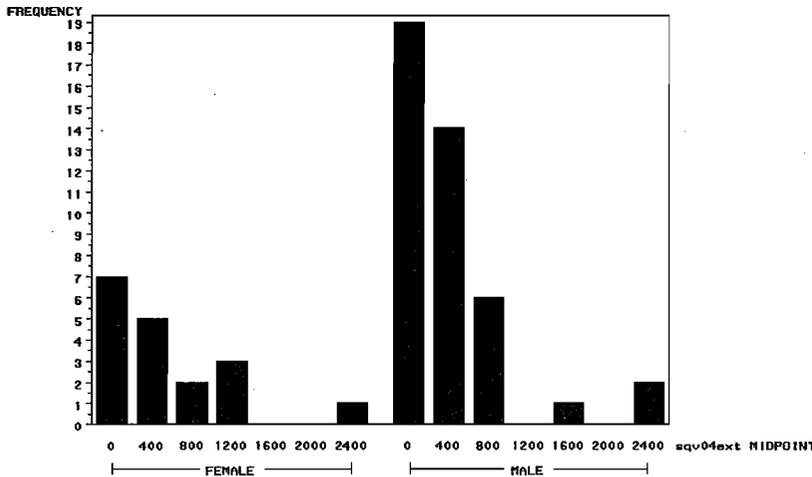
Table 11. NR15720: Week 4 SQV C<sub>min</sub> (ng/mL) by Gender.

	n	mean	SD	min	max	med	p25	p75
<b>TOTAL</b>	60	527.1	898.3	1.2	5708.7	344.3	52.8	597.4
<b>FEMALE</b>	18	549.0	636.9	1.2	2465.0	425.0	27.8	850.1
<b>MALE</b>	42	517.8	996.4	2.5	5708.7	234.2	94.9	524.4

Source: NDA 21,785, Agency analysis.

Figure 2. NR15720: Frequency of SQV C<sub>min</sub> Levels (ng/mL) by Gender.

NR15720: SQV C<sub>min</sub>



The applicant provides an analysis of GI AEs among 60 HIV-infected subjects for whom C<sub>min</sub> plasma concentrations at Week 4 were determined. The following table is provided in this NDA:

Table 12. Summary of Selected Adverse Events during Treatment + 30 Days by SQV C<sub>min</sub> Concentration at Week 4: Study NR15720 PK Sub-Population.

Preferred Term/ System Organ Class	All Patients		Grouped by [SQV] (ng/mL)							
	N = 60		Up to 53 N = 15		> 53-344 N = 15		> 344 – 597 N = 15		> 597 N = 15	
	#	%	#	%	#	%	#	%	#	%
<b>All Body Systems</b>										
Patients having ≥ 1 AE	<b>57</b>	<b>97</b>	<b>14</b>	<b>100</b>	<b>14</b>	<b>100</b>	<b>15</b>	<b>100</b>	<b>14</b>	<b>100</b>
Total # AEs	<b>459</b>		<b>60</b>		<b>151</b>		<b>115</b>		<b>133</b>	
<b>Gastrointestinal Disorders</b>										
Patients having ≥ 1 AE	42	70	9	60	12	80	11	73	10	67
Nausea	27	45	7	47	9	60	5	33	6	40
Diarrhea NOS	22	37	4	27	5	33	8	53	5	33
Vomiting NOS	12	20	2	13	3	20	2	13	5	33
Abdominal Pain NOS	10	17	0	0	5	33	3	20	2	13
Abdominal Pain Upper	5	8	3	20	2	13	0	0	0	0
Diarrhea Aggravated	2	3	0	0	2	13	0	0	0	0
<b>Total # AEs</b>	<b>78</b>		<b>16</b>		<b>26</b>		<b>18</b>		<b>18</b>	

Note: Figures in bold indicate the values obtained by the Agency's analysis of the datasets.

Source: Adapted from NDA 21,785, Module 2, Vol. 1, p. 38; Agency analysis.

The above table shows the Medical Officer's analysis of the number of AEs for all body systems. Overall, in the opinion of this Medical Officer, such minor discrepancies do not significantly affect the interpretation or the overall conclusions derived from Table 12.

The applicant extends the above analysis by examining whether or not there was a clinically significant relationship between the SQV  $C_{min}$  plasma concentration at Week 4 and the intensity (mild, moderate, severe, and life-threatening) of the most common GI AEs (abdominal pain, nausea, vomiting, and diarrhea). The applicant provides a box plot of median ( $\pm$  IQR) Week 4 [SQV]  $C_{min}$  in subjects who experienced mild ( $n = 20$ ), moderate ( $n = 8$ ), severe ( $n = 2$ ), or no AEs ( $n = 30$ ). Upon review of the plots, this Medical Officer concurs with the applicant's assertion that there are no significant differences among the median  $\pm$  IQR [SQV]  $C_{min}$  among subjects who had no AEs vs. those that experienced AEs of varying severity.

Two points are noted by this Medical Officer. First, significant variations in SQV  $C_{min}$  levels were noted among participants in the PK substudy; consistent with this observation, the IQRs for SQV levels at each intensity grade of AE were fairly large. Second, very few subjects experienced severe or life-threatening AEs. It is theoretically possible that higher SQV levels are correlated with increased AE intensity. However, the experimental validation of this hypothesis is limited by the small number of subjects in this study with at least severe AEs.

In general, the analyses of SQV  $C_{min}$  levels as performed by the Clinical and Statistical Reviewers are consistent with those of the applicant. In the opinion of this Medical Officer, there are a number of limitations to this PK substudy such as: 1) only 44 subjects in the substudy population were deemed by the study investigators to have PK parameters that were used for the investigators' analysis, mostly due to compliance-related issues; and 2) as mentioned previously, this study used a once-daily, non-approved SQV/RTV dosing regimen, which generates  $C_{min}$  levels with greater variability and which may be lower than the  $C_{min}$  levels obtained during the MaxCmin 1 study with BID dosing.

MaxCmin 1: The following paragraphs as well as Tables 13 and Figure 3 were prepared by the Statistical Reviewer. In the MaxCmin 1 safety population, 69 subjects (46.6%) in the SQV/RTV arm (ITT:  $n=148$ ) had Week 4 SQV  $C_{min}$  plasma concentration data. As defined for the NR15720 study, the safety population for MaxCmin 1 included subjects who had at least one dose of study drug and had at least one post baseline safety. The time window for the collection of data used in the following analysis was defined as Week 4  $\pm$  2 weeks from the baseline visit.

The distributions of the Week 4 SQV  $C_{min}$  levels for the PK substudy population and by gender are provided in Table 13. Female subjects had statistically significant higher SQV  $C_{min}$  than male subjects by the Kruskal-Wallis Test ( $p=0.0260$ ). The median SQV  $C_{min}$  was 821 ng/mL for males and 1562 ng/mL for females. Figure 3 displays frequencies in SQV  $C_{min}$  by gender. It is noted by this Statistical Reviewer that three females and five males had SQV  $C_{min} >2500$  ng/mL.

In the opinion of this Medical Officer, higher SQV C<sub>min</sub> levels are noted in the MaxCmin 1 study as compared to those in the NR15720 study. This difference is most likely due to the BID dosing regimen of SQV/RTV that was used in the MaxCmin 1 study.

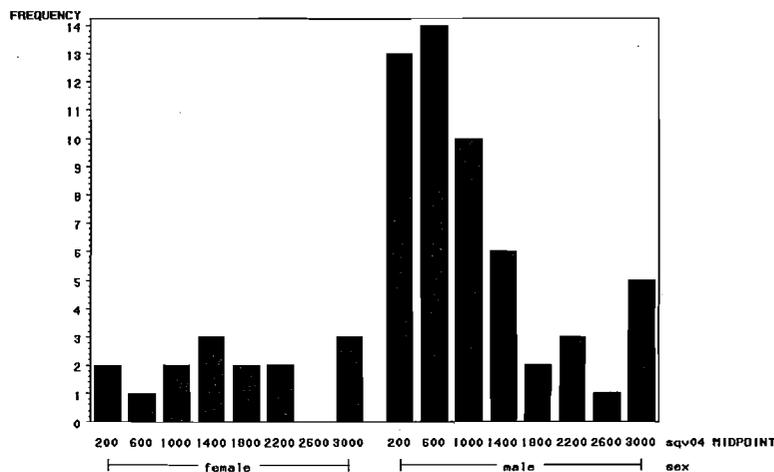
Table 13 lists the mean, standard deviation, median, range, and inter-quartiles for the entire PK-subgroup and those by gender.

Table 13. MaxCmin1: Week 4 SQV C<sub>min</sub> (ng/mL).

	n	mean	SD	min	max	med	p25	p75
<b>TOTAL</b>	69	1357.4	1304.6	164.0	6389.0	984.0	471.2	1648.3
<b>MALE</b>	54	1206.3	1226.8	164.0	6389.0	821.0	425.0	1475.0
<b>FEMALE</b>	15	1901.4	1470.9	262.0	5853.6	1562.0	896.0	2372.0

Source: Agency analysis, NDA 21,785.

Figure 3. MaxCmin 1: SQV C<sub>min</sub> Concentration (ng/mL) at Week 4 by Gender.  
 SQV C<sub>min</sub> Concentration at Week 4



Source: NDA 21,785, Agency analysis.

The applicant states that there was no evidence for a relationship between SQV C<sub>min</sub> plasma concentration and the occurrence of any AE. The applicant provides Table 16 to summarize the occurrence of the most common GI AEs (abdominal pain, nausea, diarrhea, and vomiting) among quartiles of patients with C<sub>min</sub> plasma [SQV] of ≤ 471 ng/mL, > 471 – 984 ng/mL, < 984 – 1648 ng/mL, and > 1648 ng/mL. According to the applicant, no apparent relationships were noted between the SQV C<sub>min</sub> and GI AEs.

Table 14. Summary of Selected Adverse Events during Treatment + 30 Days by SQV C<sub>min</sub> Concentration at Week 4: Study MaxCmin 1 PK Sub-Population.

Preferred Term/ System Organ Class	All Patients		Grouped by [SQV] (ng/mL)							
	N = 69		Up to 471		> 471-984		> 984 – 1648		> 1648	
	#	%	#	%	#	%	#	%	#	%
<b>All Body Systems</b>										

Patients having $\geq 1$ AE	<b>54</b>	<b>78</b>	<b>17</b>	<b>94</b>	<b>15</b>	<b>88</b>	<b>11</b>	<b>65</b>	<b>12</b>	<b>71</b>
Total # AEs	<b>273</b>		<b>66</b>		<b>58</b>		<b>71</b>		<b>81</b>	
<b>Gastrointestinal Disorders</b>										
Patients having $\geq 1$ AE	30	43	7	39	10	59	7	41	6	35
Diarrhea NOS	18	26	5	28	3	18	6	35	4	24
Nausea	11	16	1	6	4	24	4	24	2	12
Abdominal Pain NOS	10	14	3	17	3	18	2	12	2	12
Vomiting NOS	7	10	2	11	1	6	1	6	3	18
Abdominal Pain Upper	4	6	1	6	1	6	1	6	1	6
<b>Total # AEs</b>	<b>50</b>		<b>12</b>		<b>12</b>		<b>14</b>		<b>12</b>	

Note: Figures in bold indicate the values obtained by the Agency's analysis of the datasets.

Source: Adapted from NDA 21,785, Module 2, Vol. 1, p. 40; Agency analysis.

The most significant differences between the Agency's analysis and that provided by the applicant involve the number of AEs in all body systems. In the opinion of this Medical Officer, these differences do not significantly affect the applicant's interpretation of these results, i.e. no obvious trends were noted with respect to increasing SQV concentrations and the number of patients reporting AEs in each quartile. Otherwise, the analysis by this Medical Officer concurs with that of the applicant.

As was done for the NR15720 study, the applicant examined the potential relationship between Week 4 SQV  $C_{min}$  plasma concentration and the intensity of the common GI AEs (abdominal pain, nausea, vomiting, and diarrhea). The applicant reports that no such relationships were evident. The applicant provides a box plot of median ( $\pm$  IQR) Week 4 [SQV]  $C_{min}$  in subjects that experienced Grade 1 ( $n = 7$ ), Grade 2 ( $n = 9$ ), Grade 3 ( $n = 2$ ), or no AEs ( $n = 51$ ; note that no subject in the PK subpopulation experienced Grade 4 AEs). The applicant states that although subjects with Grade 3 severity appeared to have higher drug concentrations, there were only two subjects who experienced such events and their  $C_{min}$  values overlapped with  $C_{min}$  levels among subjects who did not experience severe AEs. These analyses have been reviewed by this Medical Officer who concurs with the applicant's conclusions.

#### 7.1.6 Less Common Adverse Events

The current INV HGC product label contains a listing of less common AEs that have been noted during the clinical experience with SQV use. The safety profile of SQV as shown in the five clinical studies in this NDA was similar to that described in clinical practice, medical literature, and the current INV HGC product label.

#### 7.1.7 Laboratory Findings

##### 7.1.7.1 Overview of laboratory testing in the development program

For all five studies presented in this NDA, laboratory parameters (including hematology and serum chemistry) were measured at screening, follow-up, and at protocol-specified time points during the study. Please refer to the Appendix for a summary of the laboratory testing

procedures for each of the five studies. The laboratory data from the MaxCmin 1 study have been previously reviewed by the Clinical and the Statistical reviewers in December 2003 (Zhou, 2003; Murata, 2003). From the previous review of the MaxCmin 1 study, the analysis of laboratory values is reproduced in the following sections.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

For the healthy volunteer studies, the applicant has presented data from the BP17653 study and the pooled data from studies BP17058 and BP17359. For studies involving HIV-infected patients, the applicant has provided data from subjects who received SQV as the study drug in studies NR15720 and MaxCmin 1.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

##### 7.1.7.3.1 *Analyses focused on measures of central tendency*

###### Healthy volunteer studies:

For studies BP17058 and BP17359 involving single-doses of RTV-boosted INV (as HGC or FCT), the applicant analyzed changes in laboratory values by examining the mean change in test values between each scheduled dose of boosted INV according to the randomization sequence on Days 14, 17, 20, and 23.

The applicant states that minimal changes in mean laboratory test parameter values were noted during the duration of both studies and without regard to the randomization sequences. With respect to the mean absolute values of laboratory parameters, the applicant noted slight increases in AST, ALT, and GGT levels between the last treatment phase and follow-up visits. This Medical Officer also noted slight increases in alkaline phosphatase, amylase, cholesterol, and total bilirubin levels. These changes occurred irrespective of the treatment sequence. In the context of a short study involving limited SQV/RTV dosing in healthy volunteers, this Medical Officer believes that these minor changes in laboratory values are not clinically significant.

Studies in HIV-Infected Patients: Please see the following sections for additional laboratory analyses from studies NR15720 and MaxCmin 1.

##### 7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

###### Healthy volunteer studies:

BP17653: The applicant states that the majority of subjects in this study did not exhibit a shift from baseline laboratory values during the study. Moreover, none exhibited a change from baseline of  $\geq 3$  grades according to the ACTG/AHA grading systems. One subject experienced a 2-grade shift from normal in creatine kinase levels. According to the applicant and confirmed

by this Medical Officer, none of the laboratory value shifts noted in this study was considered to be of clinical significance.

BP17058/BP17359: In the pooled safety dataset, most of the subjects did not experience a shift from baseline laboratory values or exhibited a shift from baseline of  $\leq 2$  grades according to the ACTG/AHA grading systems. Per both protocols, fasting lipid profiles were obtained during the studies.

The applicant notes that one-grade worsening in cholesterol and triglycerides were the most frequently recorded laboratory parameter shifts. A total of 32 subjects experienced a shift of  $\geq 2$  grades in laboratory test parameter values from baseline. A total of 23 subjects experienced a 2-grade shift in triglyceride levels while three subjects experienced a 2-grade shift in creatine kinase levels. Each of the following laboratory shifts of 2 grades was noted in single subjects during the study: increase in ALT, AST, and cholesterol.

The applicant also reports that three subjects experienced a shift of 3 grades from baseline in  $\geq 1$  laboratory test parameters: one had such elevations in AST and creatine kinase, another in creatine kinase, and one in triglycerides. None of these shifts were deemed by the applicant to be of clinical significance. The applicant's analyses and assessments were confirmed by this Medical Officer.

#### Studies in HIV-infected subjects:

NR15720: The applicant notes the following with respect to participants in the SQV/RTV arm:

- Lipid levels: One subject experienced a shift in triglycerides from Grade 0 at baseline to Grade 3 during the course of the study. Three out of 79 subjects whose lipid profiles were assessed during the study experienced a shift in cholesterol levels from Grade 0 at baseline to Grade 3/4 during the course of the study.
- Hematology: A total of 13 of the 81 subjects with hematology parameters drawn during the study experienced a shift from Grade 0 at baseline to Grade 3/4 in at least one hematology test parameter during the course of the study. These shifts were noted in the polymorphonuclear cell counts (seven subjects), prothrombin times (three subjects), partial prothrombin time (two subjects), and hemoglobin (one subject).
- Chemistry: Twelve out of 81 subjects with serum chemistries drawn during the study experienced a shift from Grade 0 at baseline to Grade 3/4 in at least one chemistry parameter during the course of the study. Such shifts were noted in more than one subject in the following parameters: hypoglycemia (five subjects), hyperkalemia (three subjects), and ALT (three subjects).

The line listings and tables showing these laboratory shifts were reviewed by this Medical Officer, who has confirmed the applicant's findings.

MaxCmin 1: The applicant analyzed the changes from baseline values with respect to hemoglobin, WBC count, lymphocyte count, platelet count, creatinine, AST/ALT, and amylase

at Weeks 4 and 48. The applicant has previously noted that the WBC, lymphocyte counts, and the platelet counts increased slightly (median of 8-13%) and the creatinine levels increased by 2-4% (reviewed in Murata, 2003).

The following aspects of the applicant's laboratory data analysis were noted during the December 2003 review of the data and are repeated here. First, the applicant extended the study visit windows as follows: Week 4: baseline visit-Week 10, Week 12: Week 10-21, Week 24: Week 21-33, Week 36: Week 33-45, Week 48: Week 45-60, and all data past Week 60 were censored. According to the applicant, this was done to assign a study visit to all patient visits that occurred during the study (some patients were evaluated outside the specified time windows of the study). Such extension of study windows may efficiently utilize all data collected during the study but may not clarify the time-dependent changes and trends of laboratory variables. Second, for the laboratory values in the applicant's datasets, it is unclear whether they were collected at protocol-specified scheduled visits or from non-scheduled visits and imputed/assigned to the nearest scheduled visit. Lastly, the study protocol specified analysis of only one of two transaminases (ALT or AST) at each of the protocol-specified time points.

Using the dataset provided by the applicant, the Agency's analysis as shown below included laboratory values for Weeks 4, 12, 24, 36, and 48 to determine any differences during the study:

Table 15. MaxCmin 1: Mean Absolute Values for Hematologic, Pancreatic, Renal, and Liver-related Laboratory Markers in the SQV/RTV arm.

Lab parameter	Baseline	Week 4	Week 12	Week 24	Week 36	Week 48
Hemoglobin (mmol/L)	8.47	8.38	8.47	8.6	8.6	8.7
WBC (10 <sup>9</sup> /L)	5.44	5.75	5.82	5.87	6.15	6
Platelets (10 <sup>9</sup> /L)	209	230	231	232	228	233
Lymphocytes (10 <sup>9</sup> /L)	1.75	1.92	1.86	1.91	1.87	1.94
Amylase (IU/L)	118	121	116	116	115	113
Creatinine( μmol/L)	83	86.3	86.4	83.8	85.4	84.7
Bilirubin( μmol/L)	13.7	11.9	12.2	13.1	12.9	12.4
AST (IU/L)	39.3	38.6	36.1	32.5	35.6	36.4
ALT (IU/L)	41.3	42.9	35.4	32.8	34.3	37.8

Source: LABP.xpt dataset for NDA 20828, Agency Analysis, December 2003.

For each of these laboratory parameters, the statistical significance of change from baseline values and percent change from baseline between the two treatment groups were analyzed by the Wilcoxon test. If a subject had more than one value within any of the defined time windows, the mean value was used in the statistical analysis. Given that either AST or ALT was collected at each time point according to the protocol, the decreased sample size for each of these variables may have affected the statistical analysis and interpretation of changes during the course of the study.

The applicant's analysis of values for fasting triglycerides (TG), LDL cholesterol and total cholesterol that were collected during the MaxCmin 1 study at baseline and Weeks 4 and 48 are shown in the following table:

Table 16. MaxCmin 1: Median Percent and Absolute Change from Baseline to Weeks 4 and 48 for the Three Lipid Parameters (in mmol/L) in the SQV/RTV Arm.

	Number of patients with lab values drawn at baseline (N)	Week 4 Change from Baseline (IQR) (N)	Week 48 Change from Baseline (IQR) (N)
Cholesterol Median % change	145	9% (-4-20) N=135	9% (-7-25) N=131
LDL Median % change	94	6% (-11-21) N=96	3% (-12-29) N=75
TG Median % change	150	13% (-16-68) N=137	9% (-34-41) N=135
Cholesterol Absolute change (mmol/L)	n/a	0.4 (-0.2-0.9)	0.4 (-0.4-1.1)
LDL Absolute change (mmol/L)	n/a	0.2 (-0.3-0.6)	0.1 (-0.5-0.9)
TG Absolute change (mmol/L)	n/a	0.1 (-0.3-0.8)	0.1 (-0.7-0.8)

Source: NDA 20,828, adapted from Vol. 14, p. 63, December 2003.

From these data, the applicant states that the median levels for these markers of lipid metabolism increased over the first four weeks of the study and thereafter appeared to plateau until Week 48.

The Agency's analysis of lipid parameters differs slightly from that of the applicant since the LDL and total cholesterol but not TG levels were found to be statistically different ( $p < 0.05$ ) between the treatment arms at weeks 4 and 48 (Zhou, 2003). It should be noted that the number of patients whose lipid profiles were studied vary among the time points and each of the three parameters.

#### 7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

Healthy volunteer studies: The applicant presents the following table to show the marked laboratory abnormalities recorded in the three healthy volunteer studies. Analysis of the datasets by this Medical Officer showed some differences with that presented by the applicant. However, many of these abnormalities that were identified by this Medical Officer were values just below the low range cut-off values for the four laboratory parameters. This Medical Officer agrees with the applicant's assessment that none of these events was considered to be clinically significant.

Table 17. Summary of Marked Laboratory Abnormalities in Healthy Volunteer Studies.

Parameter (Marked Reference Range)	Abnormality	# of Subjects (Agency analysis)
Lymphocytes ( $1.0 - 6.3 \times 10^9 / L$ )	Low	4 (6)
T4-lymphocytes (5 - 40%)	Low	1 (3)
Hematuria (0 - 1)	High	6 (5)

Hematocrit (0.36 – 0.60)	Low	1 (5)
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Source: NDA 21,785, Module 2, Vol. 1, p. 52; Agency analysis.

Studies in HIV-Infected Patients:

NR15720: No marked laboratory abnormalities are presented for NR15720. In the opinion of this Medical Officer, this is deemed acceptable for this NDA given the supplemental scatter plot analyses for laboratory parameters from this study (Section 7.1.7.4).

MaxCmin 1: In December 2003, the applicant has provided Table 18 to show the proportion of subjects with abnormal values of the laboratory parameters discussed in the two previous sections. In this NDA (Module 2, Vol. 1, p. 55), this table is reproduced but Week 4 data are labeled incorrectly (in the opinion of this Medical Officer) as Week 24 data. According to the applicant, the study was not designed to have statistical power to be able to detect relevant differences in these variables; thus, no formal statistical testing to detect differences between the study arms was performed.

Table 18. MaxCmin 1: Percentage of Subjects with Abnormally Low (for Hematological Parameters) and Abnormally High (for All Other Parameters) Laboratory Values at Baseline and at Weeks 4 and 48.

Laboratory Parameter	Baseline	Week 4	Week 48
Hemoglobin (< 7 mmol/L)	10	13	4
WBC count (< 3 x 10 <sup>9</sup> /L)	5	6	3
Platelet count (<150 x 10 <sup>9</sup> /L)	18	12	11
Lymphocyte Count (0.7 x 10 <sup>9</sup> /L)	11	5	5
Amylase (> 300 U/L)	3	4	2
Creatinine (130 µmol/L)	1	1	2
Bilirubin (22 µmol/L)	13	6	7
AST (>40 U/L)	21	20	19
ALT (>40 U/L)	30	30	26
Cholesterol (6.2 mmol/L)	18	27	27
LDL Cholesterol (> 3.2 mmol/L)	50	56	62
Triglycerides (> 2.3 mmol/L)	30	36	32

Source: NDA 20828 p. 14-64; Agency analysis, December 2003.

With respect to the numbers shown in Table 18, the Agency's analysis showed no significant changes/discrepancies with those of the applicant.

7.1.7.4 Additional analyses and explorations

To better define the safety profile of SQV, the applicant has analyzed the potential relationship between the SQV concentrations and changes in hepatic function test results in NR15720 and MaxCmin 1. Specifically, the applicant has examined the maximum change from baseline in selected laboratory parameters obtained in the studies and the SQV plasma concentrations (extrapolated C<sub>min</sub> levels at Week 4).

NR15720: The applicant states that scatterplots of the difference between baseline and last value for ALT, AST, amylase, total bilirubin, and cholesterol did not show any marked changes in

these parameters during the study. Furthermore, scatterplots of the maximum change from baseline for the selected laboratory parameters during the study did not show any obvious correlation between the maximum change in laboratory test parameters and SQV  $C_{min}$  plasma concentrations.

With respect to possible gender effects, scatterplot analyses of the maximum change from baseline in the selected laboratory test parameters revealed no correlation between any of the test parameters and  $C_{min}$  SQV plasma concentrations among male or female study participants.

MaxCmin 1: The applicant states that scatterplots of the difference between baseline and last value for ALT, AST, amylase, total bilirubin, and cholesterol did not show any marked changes in these parameters during the study. Moreover, scatterplots of the maximum change from baseline for the selected laboratory parameters during the study did not show any clinically relevant correlation between the maximum change in laboratory test parameters and SQV  $C_{min}$  plasma concentrations. The applicant notes that a statistically significant correlation was noted between the  $C_{min}$  concentration and the maximum change from baseline in amylase levels (correlation: 0.30;  $p = 0.0132$ ). However, the magnitude of this variation was not deemed clinically relevant by the applicant.

With respect to possible gender effects, scatterplot analyses of the maximum change from baseline in the selected laboratory test parameters revealed no correlation between any of the test parameters and  $C_{min}$  SQV plasma concentrations among male or female study participants.

These scatterplots have been reviewed by this Medical Officer, who agrees in general with the applicant's interpretation of the graphs. However, it is noted by this Medical Officer that the applicant states the following: [there was] "little evidence to suggest that SQV in single or multiple doses is associated with hepatic toxicity or has an adverse effect on laboratory parameters of hepatic function." (NDA 21,785, Module 2, Vol. 1, p. 56). In the opinion of this Medical Officer, this statement understates the points raised in the Warnings and Precautions section in the existing INV HGC label regarding the potential for hepatotoxicity especially in subjects co-infected with HBV or HCV and/or with underlying hepatic dysfunction.

#### 7.1.7.5 Special assessments

Aside from those described in the preceding sections, no special assessments of laboratory data are presented by the applicant in this NDA.

#### 7.1.8 Vital Signs

##### 7.1.8.1 Overview of vital signs testing in the development program

Please refer to the study summaries in the Appendix of this Review for brief descriptions of vital sign testing in the five clinical studies. In general, study participants underwent vital sign monitoring at screening and/or baseline study visits as well as at routine pre- and post-dosing

periods (healthy volunteer PK studies) or scheduled study or follow-up visits (NR15720 and MaxCmin 1).

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Please see the previous section.

#### 7.1.8.3 Standard analyses and explorations of vital signs data

The applicant notes that a number of subjects in the three healthy volunteer studies exhibited abnormal vital signs at times but none of these readings were deemed to be clinically significant. Line listings of vital sign readings were reviewed by this Medical Officer and the applicant's assertions were confirmed.

In studies NR15720 and MaxCmin 1, no clinically relevant changes in vital signs were noted by the applicant.

#### 7.1.8.4 Additional analyses and explorations

No additional analyses are provided by the applicant or performed by the Clinical and Statistical Reviewers.

#### 7.1.9 Electrocardiograms (ECGs)

##### 7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Please refer to the synopses of individual study reports in the Appendix of this review for summaries of ECG testing in the five clinical studies. In general, study participants underwent ECG monitoring at screening and/or baseline study visits as well as at routine pre- and post-dosing periods (healthy volunteer PK studies) or at scheduled study or follow-up visits (NR15720 and MaxCmin 1).

In the opinion of this Medical Officer, clinical experience and medical literature regarding SQV use have not identified any clinically significant effects of SQV on ECG parameters.

##### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Please see the previous section. None of the five studies involved intensive ECG monitoring and/or formal analysis of ECG parameters (e.g. QT intervals). No placebo- or active drug-controlled ECG monitoring plans/studies are described or presented in this NDA.

7.1.9.3 Standard analyses and explorations of ECG data

The applicant states that no abnormal ECG readings were identified during the course of any of the five studies that are described in this NDA.

7.1.9.4 Additional analyses and explorations

Aside from those described in the preceding sections, no other ECG monitoring/analysis plans are presented for any of the five studies in this NDA.

7.1.10 Immunogenicity

No information specific to the INV FCT formulation and immunogenicity are presented in this NDA.

7.1.11 Human Carcinogenicity

No information specific to the INV FCT and human carcinogenicity are presented nor are there new human carcinogenicity data are submitted in this NDA for INV FCT.

7.1.12 Special Safety Studies

Gender Differences in the SQV AE Profile:

Healthy volunteer studies: In study BP17653, a total of 44 AEs were reported in nine female participants and 23 AEs were reported in nine male subjects. In the pooled safety analysis for BP17058/BP17359, seven out of 120 participants were female, of which three experienced AEs. Because of the small number of female subjects that participated in these three Phase 1 PK studies, in the opinion of this Medical Officer, the clinical relevance of gender-based AE analysis is limited.

Studies in HIV-infected subjects:

NR15720: As summarized in Table 19, the applicant examined the AE profiles among 42 male and 18 female study subjects who underwent Week 4 PK monitoring:

Table 19. Study NR15720: Adverse Events: All Body Systems by Gender.

Male Subjects	All Patients N =42		Grouped by [SQV] (ng/mL)							
			Up to 53 N = 9		> 53-344 N = 14		> 344 – 597 N = 10		> 597 N = 9	
	#	%	#	%	#	%	#	%	#	%
All Body Systems										
Patients having ≥ 1 AE	41	98	9	100	14	100	10	100	8	89
Total # AEs	367		41		159		80		87	
Female Subjects	All Patients		Grouped by [SQV] (ng/mL)							

	N = 18		Up to 53 N = 6		> 53-344 N = 1		> 344 – 597 N = 5		> 597 N = 6	
	#	%	#	%	#	%	#	%	#	%
All Body Systems										
Patients having ≥ 1 AE	17	94	5	83	1	100	5	100	6	100
Total # AEs	106		22		3		35		46	

Source: NDA 21785, Module 2, Vol. 1, pp. 127-139.

Summaries of all AEs by  $C_{min}$  plasma concentrations (by quartiles: up to 53 ng/mL, < 53 – 344 ng/mL, >344 – 597 ng/mL, and > 597 ng/mL) for male and female patients in the PK substudy population are provided by the applicant. The applicant states that a slightly greater number of AEs were noted by female subjects with higher  $C_{min}$  plasma concentrations than in female subjects with low  $C_{min}$  plasma concentrations (i.e. in Table 19, note that there were 22 AEs among five subjects in the lowest quartile vs. 35 AEs in 5 subjects in the third quartile and 46 AEs in 6 subjects in the highest quartile). The applicant states that this increase was not restricted to any particular body system. Upon review of these data, in the opinion of this Medical Officer, the clinical significance of this trend is unclear since the SQV  $C_{min}$  of ≤ 53 ng/mL would be significantly less than  $C_{min}$  obtained with BID dosing of SQV/RTV. Otherwise, this Medical Officer concurs with the applicant’s assessment that no evidence for a relationship between SQV  $C_{min}$  plasma concentrations and the occurrence of AEs.

The applicant provides Table 20 to summarize the occurrence of the common GI AEs (abdominal pain, nausea, diarrhea, and vomiting) for male and female subjects in the PK substudy.

Table 20. NR15720: Summary of Selected GI AEs (During Study Treatment + 30 Days) by Gender for Patients with  $C_{min}$  Concentration at Week 4.

Preferred Term/ System Organ Class	Male Patients N = 42		Female Patients N = 18	
	#	%	#	%
Gastrointestinal Disorders				
Patients having ≥ 1 AE	30	71	12	67
Nausea	20	48	7	39
Diarrhea NOS	17	40	5	28
Abdominal Pain NOS	7	17	3	17
Vomiting NOS	7	17	5	28
Abdominal Pain Upper	3	7	2	11
Diarrhea Aggravated	2	5	-	-
Total # AEs	56		22	

Source: NDA 21,785, Module 2, Vol. 1, p. 42.

The applicant has extended the gender analysis vs. AEs by examining the relationship between the SQV  $C_{min}$  plasma concentration at Week 4 and the intensity of GI AEs (abdominal pain, nausea, vomiting, and diarrhea). The applicant states that no apparent relationship between  $C_{min}$  and GI AE intensity were noted in male or female subjects. A total of 30 subjects (females: 10, 20 males) experienced no AEs, 20 (six females, 14 males) experienced mild AEs, eight experienced moderate AEs (two females, six males), two (both males) experienced severe AEs, and none experienced life-threatening AEs.

The applicant provides time to development of AE (all AEs and selected GI AEs) in male and female subjects in the PK substudy population. The applicant notes that there appears to be a slightly higher incidence of AEs occurring earlier in the study among female subjects as compared with male subjects. However, no marked/statistically significant differences in the time-to-onset of AEs were noted between male and female subject populations.

The following paragraph and Table 21 describe the findings of the Statistical Reviewer. Table 21 lists the mean, standard deviation, median, range, and inter-quartiles for the entire PK subgroup and those by gender. The PK-subgroup had a total of 532 AEs, 150 (28.2%) of which were GI-related AEs. Female subjects had greater total number of AEs, including GI-related and non-GI-related AEs, than did male subjects. For example, female subjects had a median of 7 AEs, versus a median of 5.5 AEs for male subjects. However, none of the gender-related differences in the number of AEs were statistically significant ( $p > 0.24$ ).

Table 21. NR15720: Gender Difference in Selected Summary Statistics for Adverse Events: PK Subgroup (n=60)\*.

	GENDER	med	min	max	p25	p75	mean	std	p-value
Total # AE	Total	7	0	47	2.5	11.5	8.87	8.85	
	Male	5.5	0	28	2	9	6.56	6.38	0.2407
	Female	7	0	47	3	13	9.86	9.62	
Total # GI AE	Total	1.5	0	12	1	3.5	2.50	2.87	
	Male	1	0	11	0	2	1.94	2.69	0.2594
	Female	2	0	12	1	4	2.74	2.94	
Total # Non-GI AE	Total	1.5	0	12	1	3.5	2.50	2.87	
	Male	1	0	11	0	2	1.94	2.69	0.3309
	Female	2	0	12	1	4	2.74	2.94	

\* N=18 for female and 42 for male. P-value- by Kruskal-Wallis Test.

Source: NDA 21,785, Agency analysis.

The Statistical Reviewer conducted analyses to examine gender difference and other prognostic factors in time course of AE using the stepwise Cox proportional hazard model. For the PK subgroup, the following five variables were considered: SQV  $C_{min}$  at Week 4; CD4 cell count at baseline; gender; baseline stratification indicator for HIV-1 RNA; and baseline failure indicator. None of the above baseline variables and gender had significant contribution for prediction of development of AE at a significance level of  $p < 0.25$ .

MaxCmin 1: The applicant presents gender analysis based on 54 male and 15 female subjects who underwent PK monitoring at Week 4.

Table 22. MaxCmin 1: Adverse Events: All Body Systems by Gender.

Male Subjects	All Patients N = 54		Grouped by [SQV] (ng/mL)							
			Up to 471 N = 16		> 471 – 984 N = 14		> 984 – 1648 N = 13		> 1648 N = 11	
	#	%	#	%	#	%	#	%	#	%
All Body Systems										
Patients having $\geq 1$ AE	40	74	15	94	11	79	7	54	7	64
Total # AEs	149		48		26		43		32	
Female Subjects	All Patients N = 15		Grouped by [SQV] (ng/mL)							
			Up to 471		> 471 – 984		> 984 – 1648		> 1648	
	#	%	#	%	#	%	#	%	#	%

			N = 2		N = 3		N = 4		N = 6	
	#	%	#	%	#	%	#	%	#	%
All Body Systems										
Patients having ≥ 1 AE	14	93	2	100	3	100	4	100	5	83
Total # AEs	80		10		20		14		36	

Source: NDA 21785, Module 2, Vol. 1, pp. 142 - 152.

Summaries of all AEs by  $C_{min}$  plasma concentrations (by quartiles: up to 471 ng/mL, > 471 – 984 ng/mL, > 984 – 1648 ng/mL, and > 1648 ng/mL) for male and female patients in the PK substudy population are provided by the applicant; these line listings and tables have been reviewed by this Medical Officer. The applicant states that no relationship was noted between the occurrence of any AE and SQV plasma concentration in male or female subjects; this is confirmed by this Medical Officer. However, the applicant does note that a higher percentage of female subjects reported AEs (93%; 14 out of 15) during the course of the study than did male patients (74%; 40 out of 54). This difference was noted in the frequency of most commonly reported GI AEs; 60% (9 out of 15) female subjects reported at least one GI AE as compared to 39% (21 out of 54) male subjects. This is shown in Table 23 that summarizes the occurrence of common GI AEs (abdominal pain, nausea, diarrhea, and vomiting) by gender:

Table 23. MaxCmin 1: Summary of Selected GI AEs (During Study Treatment + 30 Days) by Gender for Patients with  $C_{min}$  Concentration at Week 4.

Preferred Term/ System Organ Class	Male Patients N = 54		Female Patients N = 15	
	#	%	#	%
Gastrointestinal Disorders				
Patients having ≥ 1 AE	21	39	9	60
Diarrhea NOS	14	26	4	27
Nausea	14	26	4	27
Abdominal Pain NOS	5	9	5	33
Abdominal Pain Upper	3	6	1	7
Vomiting NOS	2	4	5	33
Total # AEs	31		19	

Source: NDA 21,785, Module 2, Vol. 1, p. 45.

The applicant presents additional gender-based analysis with regard to SQV plasma  $C_{min}$  levels at Week 4 and the intensity of GI AEs (abdominal pain, nausea, vomiting, and diarrhea). The applicant notes that female subjects had higher median  $C_{min}$  levels than did male patients for GI AEs of all grades, but no evidence of a relationship between  $C_{min}$  plasma concentration and GI AE intensity was noted in either male or female subjects.

#### Statistical Reviewer's Analysis of Gender Effects on the Safety Profile - MaxCmin 1

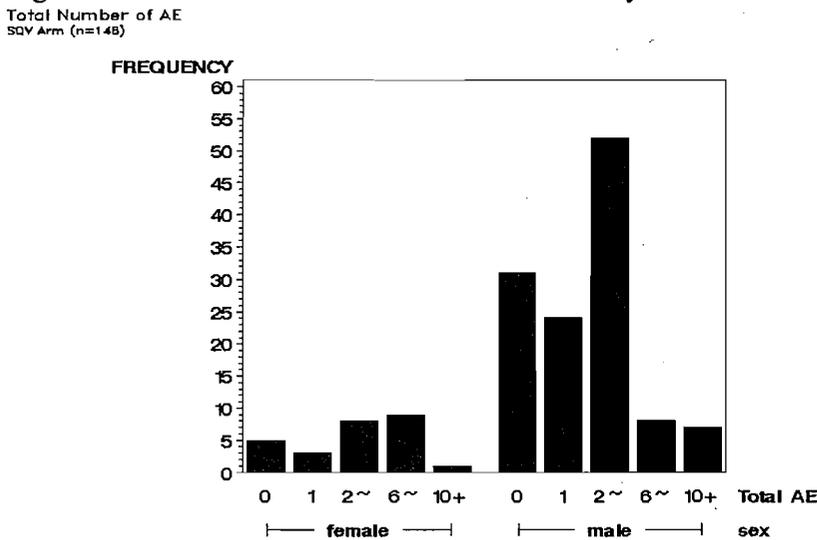
For each subject in the SQV/RTV arm (n = 148) and in the PK substudy (n = 69), this Statistical Reviewer computed the number of total AEs, GI-related AEs, selected GI-related AE (as defined by the applicant: nausea, vomiting, diarrhea, and abdominal pain), and Grade 3/4 AEs. The results were classified according to gender and are shown in Tables 24 and 25.

**SQV/RTV Arm:**

In the MaxCmin1 study, the SQV/RTV arm had a total of 424 AEs that developed within 30 days from the date of termination of the study drug treatment post baseline study visit. The ratio of GI-related AEs (as defined by the applicant) versus non-GI-related AE was 40.9% (123/301). Among 55 Grade 3 /4 AEs observed during this period, the ratio of GI-related AE versus non-GI-related AE was 22.2% (10/45). In addition, there were 88 (20.8%) GI-related AEs, eight of which were reported as Grade 3 or 4.

The distributions of total number of AEs by gender are included in Figure 4. A total of 88/122 (70.5%) male subjects and 12/26 (46.2%) female subjects had not developed AEs during this study period (Chi Square = 5.68, p = 0.0172). Two AE summary statistics had significant gender differences. The median number of GI-related AEs was 4.5 for female and 2 for the male subjects (p = 0.0004 by the Kruskal-Wallis test). For non-GI AEs, female subjects had a median of 3.5 AEs, significantly greater than median of 1 AE for male subjects (p = 0.0020). There were no significant gender differences for rest of the summary AE statistics, including the number of GI-related AE or Grade 3 /4 AE. Additional analyses of AEs by baseline characteristics and gender for the MaxCmin 1 study (entire SQV/RTV population and those in the PK substudy) are presented below.

Figure 4. MaxCmin 1: Distribution of All AEs by Gender.



Source: Agency analysis, NDA 21,785.

The median values of the six AE variables for female are all greater or equal to those for male subjects. In particular, females developed more AEs overall and selected GI-related Grade 3 /4 AEs than subjects in the male population (p < 0.01). In addition, this Statistical Reviewer notes the following points:

- The total number of Grade 3 /4 AEs is significantly correlated with the total number of AEs by the Spearman correlation coefficient for male ( $r = 0.3945$ ,  $p < 0.0001$ ) and female subgroups ( $r = 0.4902$ ,  $p < 0.0110$ ).
- Overall, the total number of Grade 3 /4 AEs is significantly correlated with the total number AEs by the Spearman correlation coefficient ( $r = 0.3994$ ,  $p < 0.0001$ ).
- Female subjects had a median of 4.5 AEs, significantly greater than a median of 2 AEs for male subjects ( $p = 0.0125$ , by the Kruskal-Wallis test).
- A total of 25 out of 122 (20.5%) male subjects and 5 out of 26 (19.2%) females had Grade 3 /4 AEs during this study period. No gender difference was found with respect to the incidence of Grade 3/4 AEs by gender.

Table 24. MaxCmin 1: Gender Difference in Selected Summary Statistics for Adverse Events: SQV/RTV Arm (n=148)\*

	GENDER	n	med	min	max	p25	p75	mean	std	p-value
Total # AE	Total	148	2	0	16	1	4	2.86	3.31	
	Male	122	2	0	15	0	3	2.57	3.15	<b>0.0152</b>
	Female	26	4.5	0	16	1	6	4.27	3.74	
Total Grade 3 /4 AE	Total	148	0	0	6	0	0	0.37	0.98	
	Male	122	0	0	6	0	0	0.39	1.05	0.8799
	Female	26	0	0	2	0	0	0.27	0.60	
Total # GI AE	Total	148	0	0	9	0	1	0.83	1.43	
	Male	122	0	0	9	0	1	0.81	1.45	0.4739
	Female	26	0	0	5	0	1	0.92	1.32	
Total Grade 3 /4 GI AE	Total	148	0	0	4	0	0	0.07	0.38	
	Male	122	0	0	4	0	0	0.07	0.40	0.4429
	Female	26	0	0	1	0	0	0.08	0.27	
Total # Non-GI AE	Total	148	1	0	16	0	3	2.03	2.70	
	Male	122	1	0	14	0	2	1.75	2.47	<b>0.0020</b>
	Female	26	3.5	0	16	1	4	3.35	3.32	
Total Grade 3 /4 Non-GI AE	Total	148	0	0	6	0	0	0.30	0.85	
	Male	122	0	0	6	0	0	0.33	0.91	0.6554
	Female	26	0	0	2	0	0	0.19	0.49	
Total # Selected GI AE	Total	148	0	0	5	0	1	0.59	1.08	
	Male	122	0	0	5	0	1	0.55	1.08	0.1135
	Female	26	0	0	3	0	1	0.81	1.10	
# Selected GI AE / Grade 3/4	Total	148	0	0	4	0	0	0.05	0.36	
	Male	122	0	0	4	0	0	0.05	0.38	0.1868
	Female	26	0	0	1	0	0	0.08	0.27	

Source: Agency Analysis, NDA 21,785.

Analyses for baseline factors that may be correlated with AEs were performed for the entire study population who received SQV/RTV (n = 148) and the results are summarized in Table 26. Female subjects had lower median CD4 cell count (i.e. 18 cells/mm<sup>3</sup> less than the median cell count of 186 cells/mm<sup>3</sup> in male subjects,  $p = 0.0550$ ). Female had a higher median viral load (4.34 log<sub>10</sub> copies/mL) as compared to 3.49 log<sub>10</sub> copies/mL for male subjects; however, this difference was not statistically significant. Gender differences were observed for the number of antiretroviral drugs at study entry and number of PI at study entry, with p-values around 0.1. More female subjects were PI-naïve than were in the male population (69.2% (18/26) versus 53.3% (65/122),  $p = 0.1367$ , Chi-square test). Similarly, more female subjects were ART-naïve than the male population (61.5% (16/26) versus 43.4% (53/122),  $p=0.0931$ , Chi-square test).

PK Substudy Population:

A total of 216 AEs were reported during study drug treatment period + 30 days following cessation of study treatment. Of these AEs, 67 (31.0%) were GI-related AE, and 20.3% were selected GI-related AE. Among 22 Grade 3 /4 AE, 19 (86%) were non-GI-related AE. The following points are noted by this Statistical Reviewer regarding AEs and SQV C<sub>min</sub> at Week 4, and with respect to gender comparisons:

- A total of 18/54 (33.3%) male subjects and 1/15 (6.7%) female subjects did not develop AEs during this study period (Chi Square = 4.18, p = 0.04). Female subjects had a median of 6 AEs, which was greater than that in males in whom a median of 1 AE was observed; this difference was statistically significant (p = 0.0004 by the Kruskal-Wallis test).
- Using the applicant's definition of GI-related AEs, there were 48 (21.2%) such events among 216 AEs. With regard to such AEs, female subjects had a median of 1 AE and males had a median of 0 AE (p = 0.0617 by the Kruskal-Wallis test).
- There were 9/54 (16.7%) male subjects and 3/15 (20%) female subjects who reported Grade 3/ 4 AEs (p > 0.05 by the Chi-square test).
- The total number of Grade 3 /4 AEs is highly correlated with total number of AEs for the entire population (r = 0.4297, p = 0.0002), and in the male population (r = 0.4598, p = 0.0005), but not in the female subgroup (p > 0.05).
- Overall, the SQV C<sub>min</sub> at Week 4 is not significantly correlated with total number of AEs or number of Grade 3 /4 AE, by the Spearman correlation coefficient. The only significant result is for females in which higher SQV C<sub>min</sub> at Week 4 is highly correlated with total number of Grade 3 /4 AEs.
- In female and male subgroups, the total number of AEs is not correlated with the Week 4 SQV C<sub>min</sub> levels.

Table 25. MaxCmin 1: Gender Difference in Selected Summary Statistics for Adverse Events: PK Subgroup (n=69)\*.

	GENDER	med	min	max	p25	p75	mean	std	p-value
Total # AE	Total	2	0	16	0	5	3.13	3.81	
	Male	1	0	15	0	3	2.41	3.48	0.0004
	Female	6	0	16	4	7	5.73	3.92	
Total Grade 3 /4 AE	Total	0	0	6	0	0	0.32	0.92	
	Male	0	0	6	0	0	0.31	0.97	0.7242
	Female	0	0	2	0	0	0.33	0.72	
Total # GI AE	Total	0	0	9	0	1	0.93	1.57	
	Male	0	0	9	0	1	0.83	1.56	0.2089
	Female	1	0	5	0	3	1.27	1.58	
Total Grade 3 /4 GI AE	Total	0	0	1	0	0	0.04	0.21	
	Male	0	0	1	0	0	0.02	0.14	0.0555
	Female	0	0	1	0	0	0.13	0.35	
Total # Non-GI AE	Total	1	0	16	0	3	2.20	3.16	
	Male	1	0	14	0	2	1.57	2.70	0.0001
	Female	4	0	16	3	5	4.47	3.74	
Total Grade 3 /4 Non-GI AE	Total	0	0	6	0	0	0.28	0.86	
	Male	0	0	6	0	0	0.30	0.92	0.7751
	Female	0	0	2	0	0	0.20	0.56	
Total # Selected GI AE	Total	0	0	4	0	1	0.64	1.06	
	Male	0	0	4	0	1	0.50	0.95	0.0521
	Female	1	0	3	0	3	1.13	1.30	
# Selected GI AE / Grade 3/4	Total	0	0	1	0	0	0.03	0.17	
	Male	0	0	0	0	0	0.00	0.00	0.0069
	Female	0	0	1	0	0	0.13	0.35	

\*. N=69. P-value- by Kruskal-Wallis Test.

Source: NDA 21,785, Agency analysis.

**PK Subgroup:** Table 26 lists the mean, standard deviation, median, range, and quartiles by gender for the PK subgroup. Kruskal-Wallis tests were used for the comparisons of these factors by gender. Female subjects had lower median CD4 cell counts (134 cells/mm<sup>3</sup>) and greater median viral loads (4.52 log<sub>10</sub> copies/mL) than did male subjects (median CD4 cell count: 214 cells/mm<sup>3</sup> and the median viral load: 2.11 log<sub>10</sub> copies/mL). However, these differences were not statistically significant. In contrast, gender differences were observed with respect to the number of antiretroviral drugs at study entry and number of PIs at entry, with p-values around 0.07. More female subjects were PI-naïve than the male population: 66.7% (10/15) versus 38.9% (21/54), (p = 0.0557, Chi-square test). In addition, more female subjects were ART-naïve than in the male population, i.e. 66.7% (10/15) versus 31.5% (17/54) (p = 0.0135, Chi-square test).

Table 26. MaxCMin 1: Gender Difference in Baseline Variables\*.

	GENDER	N	med	min	max	p25	p75	mean	std	p-value
<b>1. SQV Arm (n=148)</b>										
<b>CD4 at baseline</b>	Total	144	146.00	0.00	1100.00	0.70	331.00	206.39	227.23	0.0550
	Male	118	186.00	0.00	1100.00	0.80	369.00	225.18	233.61	
	Female	26	18.00	0.08	604.00	0.58	162.00	121.14	175.27	
<b>Baseline HIV-1 RNA in log<sub>10</sub></b>	Total	148	3.95	1.69	5.88	1.69	5.05	3.56	1.60	0.3145
	Male	122	3.49	1.69	5.88	1.69	4.94	3.50	1.61	
	Female	26	4.34	1.69	5.81	1.98	5.16	3.83	1.57	
<b># of HIV Drugs at entry</b>	Total	148	1	0	7	0	3	1.30	1.50	0.1031
	Male	122	1	0	7	0	3	1.39	1.54	
	Female	26	0	0	3	0	2	0.88	1.24	
<b># of PIs at entry</b>	Total	148	0	0	3	0	1	0.53	0.66	0.1242
	Male	122	0	0	3	0	1	0.57	0.68	
	Female	26	0	0	2	0	1	0.35	0.56	
<b>2. PK-subgroup (n=69)</b>										
<b>CD4 at baseline</b>	Total	162.00	0.13	772.00	0.69	375.00	216.71	209.66		0.7489
	Male	214.00	0.13	772.00	0.58	400.00	229.60	213.72		
	Female	134.00	0.58	604.00	2.00	293.00	170.27	193.98		
<b>Baseline HIV-1 RNA in log<sub>10</sub></b>	Total	3.02	1.69	5.88	1.69	4.84	3.30	1.64		0.1367
	Male	2.11	1.69	5.88	1.69	4.75	3.15	1.63		
	Female	4.52	1.69	5.81	1.69	5.31	3.85	1.65		
<b># of HIV Drugs at entry</b>	Total	1	0	5	0	3	1.45	1.46		0.0735
	Male	1	0	5	0	3	1.59	1.46		
	Female	0	0	3	0	3	0.93	1.39		
<b># of PIs at entry</b>	Total	1	0	3	0	1	0.67	0.70		0.0729
	Male	1	0	3	0	1	0.74	0.71		
	Female	0	0	2	0	1	0.40	0.63		

\*. P-value- by Kruskal-Wallis Test.

Source: NDA 21,785, Agency analysis.

Table 27. MaxCmin 1: Correlation between Baseline Variables and AE Frequency \*.

	CD4+ Cell Count at Baseline				Number of PI-drugs Prior to Entry			
	SQV Arm (n=144)		PK-subgroup (n=69)		SQV Arm (n=148)		PK-subgroup (n=69)	
	r	p-value	r	p-value	r	p-value	r	p-value
<b>Total # AE</b>	-0.1036	0.2165	-0.0636	0.6039	<b>-0.2240</b>	<b>0.0062</b>	<b>-0.3100</b>	<b>0.0095</b>
<b>Total Grade 3 /4 AE</b>	0.0618	0.4622	0.0649	0.5962	-0.1575	0.0558	-0.2235	0.0649
<b>Total # GI AE</b>	<b>-0.1741</b>	<b>0.0369</b>	-0.1507	0.2166	-0.0803	0.3319	-0.0841	0.4920
<b>Total Grade 3 /4 GI AE</b>	-0.0269	0.7497	0.0036	0.9768	-0.0754	0.3626	-0.1026	0.4017
<b>Total # Non-GI AE</b>	-0.0805	0.3378	0.0036	0.9768	<b>-0.2303</b>	<b>0.0049</b>	<b>-0.3262</b>	<b>0.0062</b>
<b>Total Grade 3 /4 Non-GI AE</b>	0.0627	0.4555	0.0653	0.5942	-0.1542	0.0613	<b>-0.2520</b>	<b>0.0367</b>
<b>Total # Selected GI AE</b>	<b>-0.2443</b>	<b>0.0032</b>	<b>-0.2470</b>	<b>0.0407</b>	-0.1542	0.0613	-0.1385	0.2585
<b># Selected GI AE / Grade %</b>	0.0072	0.9320	0.0607	0.6201	-0.0249	0.7635	-0.0336	0.7842
<b>Baseline HIV-1 RNA</b>	<b>-0.3117</b>	<b>0.0001</b>	<b>-0.3235</b>	<b>0.0067</b>	<b>-0.8963</b>	<b>0.0001</b>	<b>-0.7795</b>	<b>0.0001</b>
<b>#PI drug at Baseline</b>	<b>0.2118</b>	<b>0.0108</b>	0.1821	0.1342	na	na	na	Na
<b># ART drug at Baseline</b>	<b>0.1737</b>	<b>0.0374</b>	0.2183	0.0716	<b>0.7568</b>	<b>0.0001</b>	<b>0.7396</b>	<b>0.0001</b>
<b>SQV Cmin at Week 4</b>	na	na	-0.0463	0.7054	Na	Na	<b>-0.3889</b>	<b>0.0010</b>

Source: NDA 21,785, Agency analysis.

The gender comparisons of six AE quantities are summarized in second part of Table 26. The median values of the six AE variables for females are all greater than or equal to those for male subjects. In particular, females developed more AEs than did males ( $p = 0.0152$ ).

In the opinion of the Statistical Reviewer, the above results indicate that: 1) the female population may be at a slightly more advanced stage of HIV-1 infection than the male population; and 2) female subjects in the SQV/RTV population as well as in the PK substudy may have received ART/PI treatment later than male subjects in the corresponding groups.

Time to Onset of AE: Entire SQV/RTV Arm (n = 148): The associations between gender and other baseline prognostic factors and time course of development of AE were also investigated using the stepwise Cox proportional hazard model for all subjects in the SQV/RTV arm. In these analyses, five variables are included: gender; CD4 at baseline; baseline HIV-1 RNA in  $\log_{10}$  copies/mL; baseline ART naïve or not; and baseline PI-naïve or not. A baseline factor with a significant level of  $< 0.25$  was reported.

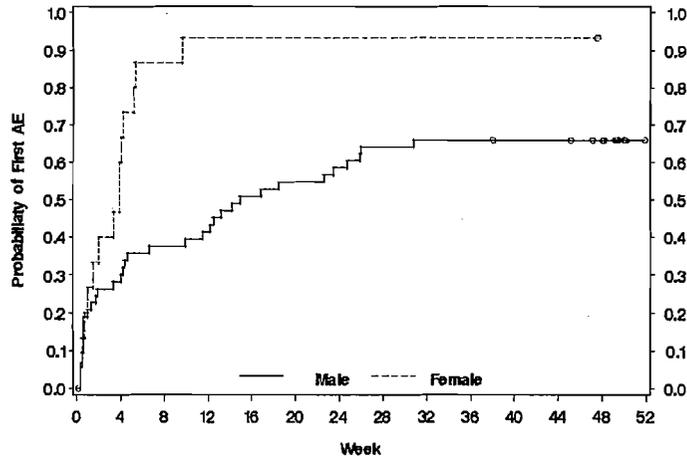
This Statistical Reviewer notes the following results:

- Time to first AE is associated with gender at  $p=0.0024$ .
- Time to first GI-related AE is associated with CD4 cell count at baseline with  $p=0.0394$ .
- Time to first Selected GI-related AE is associated with CD4 cell count at baseline ( $p = 0.0071$ ) and gender ( $p = 0.2439$ ). Gender was removed from the equation because of the conditional  $p = 0.2439$  exceeds the cutoff of  $p = 0.15$ .

Time to Onset of AE for PK subgroup (n = 69): This Statistical Reviewer repeated the Kaplan-Meier (K-M) approach that was used by the applicant to analyze time to first onset of AE and that of GI-related AE (as defined by the applicant as nausea, vomiting, abdominal pain, or diarrhea; or all GI-coded AEs). Female subjects had a shorter time to first AE (all body systems) or selected GI-related AE than did male subjects ( $p = 0.0013$  or  $p = 0.0817$ , respectively, by the log-rank test). However, gender is not associated with all GI AEs ( $p > 0.2$ ). Figures 5 – 7 are K-M curves by gender.

Figure 5. MaxCmin 1 PK Substudy: Time-to-AE.

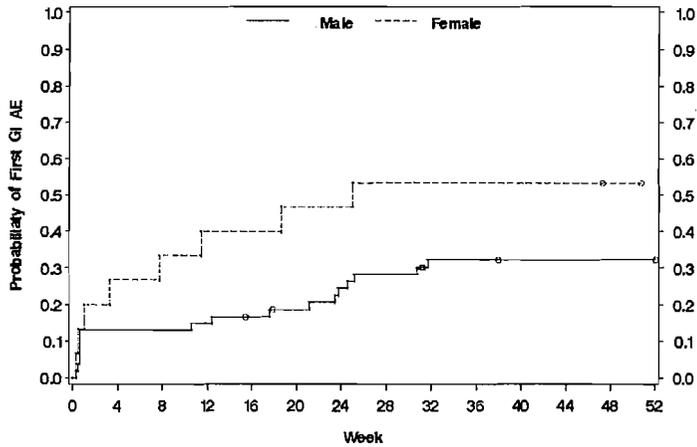
MaxCmin1: Time to First Onset of Adverse Event  
Patients with SQV Concentration at Week 4 (n=69)



Source; NDA 21,785, Agency analysis.

Figure 6. MaxCmin 1 PK Substudy: Time-to Selected GI AE by Gender.

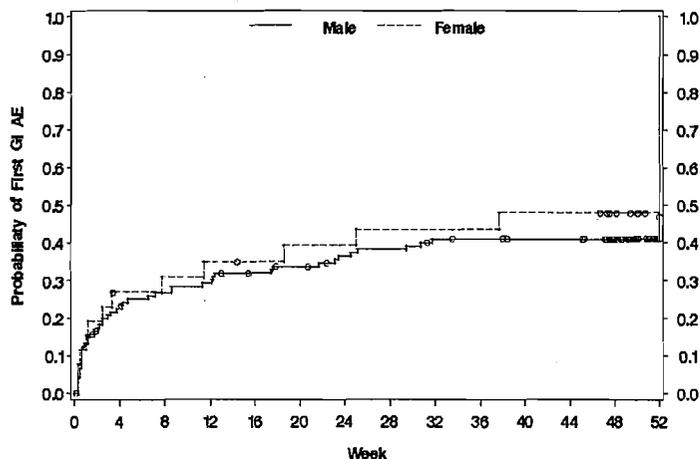
MaxCmin1: Time to First Onset of GI Adverse Event  
Patients with SQV Concentration at Week 4 (n=69)



Source: NDA 21,785, Agency analysis.

Figure 7. MaxCmin 1 PK Substudy: Time-to GI (Any GI) AE by Gender.

MaxCmin1: Time to First Onset of GI (all) Adverse Event  
Patients with SQV Concentration at Week 4 (n=69)



Source: NDA 21,785, Agency analysis.

Clinical and Statistical Summary: Taken together, the above analyses suggest that there is a statistically significant trend towards female study subjects in the PK subpopulation experiencing AEs (all systems and select GI AEs) at an earlier time during the study than male subjects. Furthermore, female subjects appear to experience more AEs than male subjects. However, in the opinion of this Medical Officer, a number of issues may be confounding the interpretation of the results. Perhaps most significantly, this observation is based on limited data involving only 15 female subjects. In addition, there was limited PK sampling at Week 4 and no other PK sampling points to verify that SQV  $C_{min}$  levels were maintained during the study. Furthermore, no consideration is given to the effect of demographics, history or antiretroviral treatment (note that a greater proportion of females were treatment- or PI-naïve than in the male population), concomitant meds/antiretroviral agents, and underlying medical conditions. Thus, in the opinion of this Medical Officer, the gender-related effects on AE profiles of participants in the MaxCmin 1 PK substudy are noted, but the clinical significance of the above observations are unclear at this time with limited data. The possible effects of gender and SQV exposure should be explored as postmarketing commitments (see Section 9.3.2).

Because of dataset issues (e.g. inconsistent names of antiretroviral agents entered into the datasets) noted during the December 2003 review of the MaxCMin 1 study, the numbers of subjects in the SQV/RTV arm who were deemed by the applicant to be treatment-naïve (n = 42) or PI-naïve (n = 68) at study entry were not confirmed by the Clinical or Statistical Reviewers. For this NDA review, the Statistical Reviewer used the variable 'BASEDATE' in the revised datasets DEMO.XPT and MEDO.XPT to determine whether or not subjects in the MaxCmin 1 study were treatment-naïve or PI-naïve. Time windows of 30, 60, 90, and 120 days before the BASEDATE were used as cutoffs and the number of treatment-naïve or PI-naïve subjects did not change significantly. This manipulation ensures the status of antiretroviral exposure at the time of study entry since the medication history is compared to a specific study date. Based on this analysis, the number of subjects in the SQV/RTV arm who were treatment-naïve and PI-naïve were 69 and 83, respectively, as identified by this Statistical Reviewer. It is the collective

opinion of the Clinical and Statistical Reviewers that based on the information reviewed for this NDA, the differences in the Agency's analysis and that of the applicant with regard to antiretroviral treatment history of the patients in the SQV/RTV arm do not significantly affect the conclusions presented in this Joint Clinical/Statistical Review.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Based on clinical experience since the approval of INV HGC and FTV, SQV has not been associated with any clinically significant withdrawal phenomena or abuse potential. In this NDA, the applicant states that there is no information specific to the INV FCT formulation and cites the currently approved product label for INV HGC for additional information.

#### 7.1.14 Human Reproduction and Pregnancy Data

Pregnancies reported during the clinical studies are summarized in the Appendix. With respect to use in pregnancy and lactation, the applicant states that there is no information specific to the INV FCT formulation and cites the currently approved product label for INV HGC for additional information.

#### 7.1.15 Assessment of Effect on Growth

All the studies that are presented in this NDA have been conducted in adults. Thus, in this NDA, there are no formal assessments of the effect of SQV on growth parameters. It should be noted that SQV has not been approved for use in children and the pediatric written request for SQV has recently been resubmitted in November 2004. To date, there are limited safety and efficacy data on the use of SQV in the pediatric population.

#### 7.1.16 Overdose Experience

The applicant states that there is no information specific to the INV FCT formulation and cites the currently approved product label for INV HGC for additional information.

#### 7.1.17 Postmarketing Experience

The applicant states that since the INV 500 mg FCT is not licensed in any region at the time of the NDA filing, there are no postmarketing experiences for the proposed product.

The postmarketing experience for the co-administration of RTV with INV HGC or FTV was recently reviewed by the Division for the approval of INV HGC or FTV 1000 mg /RTV 100 mg BID dosing regimens. In December 2003, a consultation to the ODS was requested by this Medical Officer for review and analysis of the Agency's Adverse Event Reporting System (AERS) based safety profile of SQV/RTV combination regimens.

In brief, a total of 706 cases of AEs were identified when AERS was searched for all AEs reported to the FDA with both SQV (as INV HGC or FTV) and RTV were listed as suspected drugs. Clinical records involving specific AEs of interest, including hepatotoxicity, lipid abnormalities, osteonecrosis, pancreatitis, and renal failure were examined. No unexpected AEs beyond those previously described with SQV or RTV use were identified. Following the recommendations from ODS, the SQV product labels now bear: 1) a Precaution regarding increased levels of triglycerides and the potential to develop pancreatitis; and 2) a statement regarding the potential for substantial increase of triglyceride and cholesterol levels upon combined use of SQV and RTV.

For this NDA, the ODS consult report from December 2003 was reviewed by this Medical Officer to determine whether or not there was a clinically significant relationship between AEs associated with SQV/RTV co-administration and gender. Of the 78 unduplicated hepatic events (involving 60 males, 15 females, and three of unknown gender) eight described hepatic failure (including six males and one female). Of the 11 unduplicated cases of bone necrosis, eight involved males and three involved females. Of the four cases of osteoporosis, three involved males and one involved a female subject. Taken together, there appears to be no compelling evidence that previously reported AERS events associated with SQV/RTV predominantly involve females (and thus would correlate with increased SQV exposure among females as compared to males).

This interpretation of the AERS safety database has several limitations, including the patient population (i.e. unknown baseline gender demographics, early HIV clinical studies of SQV involved predominantly male subjects), and possible contributions (e.g. additive or synergistic) effects of concomitant antiretroviral and other medications.

## **7.2 Adequacy of Patient Exposure and Safety Assessments**

### **7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**

Please refer to Table 1, which summarizes the clinical data sources that were reviewed in this study. Also, for detailed information on individual studies, please refer to the Appendix for summaries of the studies.

#### **7.2.1.1 Study type and design/patient enumeration**

See 7.2.1 above.

#### **7.2.1.2 Demographics**

See 7.2.1 above.

### 7.2.1.3 Extent of exposure (dose/duration)

See 7.2.1 above.

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The literature citation (Fletcher, et al., 2004) and the ODS consultation on AEs associated with SQV/RTV regimens are the two major sources of secondary clinical data.

### 7.2.2.1 Other studies

Not applicable; no other studies besides those listed in Table 1 were reviewed.

### 7.2.2.2 Postmarketing experience

Please refer to the summary of the ODS safety review from 2003.

### 7.2.2.3 Literature

See Section 7.2.2. above.

## 7.2.3 Adequacy of Overall Clinical Experience

It is the opinion of this Medical Officer that in this NDA, the overall clinical experience to support the approval of the INV FCT has been presented by the applicant. This is taking into consideration the previous approval and extensive clinical experience since the approval of SQV as INV HGC (1995) and FTV (1997).

With respect to the new formulation of SQV as INV 500 mg FCT, the limited clinical experience in healthy volunteers is consistent with previously described AE profiles associated with SQV use. Based on the bioavailability and bioequivalence data, the exposure of SQV following administration of INV FCT 1000 mg/RTV 100 mg is expected to be similar to those from SQV (as INV HGC or FTV) 1000 mg/RTV 100 mg BID. Thus, the AE profile of INV FCT is expected to be similar to those described for INV HGC and FTV in general.

To evaluate the possibility that increased SQV exposure among female subjects may be associated with altered AE profile for SQV, the applicant's analysis of AEs among participants in PK substudies of NR15720 and MaxCmin 1 were reviewed by the Clinical and Statistical Reviewers. No significant association was noted between Week 4 SQV  $C_{min}$  levels and intensity or frequency of AEs. With regard to gender, females in MaxCmin 1 experienced more AEs and shorter time to AEs (all AEs, or selected GI-related AEs) than did males. Given the limitations of these safety analyses, including the relatively small sample size of the PK substudy population as well as differences in baseline characteristics among female and male participants, no labeling changes are recommended at this time. To further address these issues, the applicant will be asked to fulfill postmarketing commitments (see Section 9.3).

#### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new PharmTox data are presented in this NDA; please refer to Dr. Wu's PharmTox review for additional details.

Additional in vitro testing data of the antiretroviral activity of SQV have been requested from the applicant as a postmarketing commitment from December 2003 NDA review. Please refer to Dr. Battula's Micro review for additional details.

#### 7.2.5 Adequacy of Routine Clinical Testing

With respect to healthy volunteer studies, the extent of routine clinical testing (clinical laboratories, vital signs, ECGs, AE monitoring) are deemed by this Medical Officer to be adequate.

For the MaxCmin 1 study, the adequacy of routine clinical testing was reviewed in December 2003. In brief, the extent of routine clinical testing was deemed by this Medical Officer to be adequate.

For the NR15720 study, the routine clinical testing as presented in this NDA and solely to provide supportive safety data for INV FCT is deemed adequate by this Medical Officer.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please refer to the ClinPharm review of this NDA by Dr. DiGiacinto. As postmarketing commitments for the December 2003 approval of the SQV/RTV 1000 mg/100 mg dosing regimen, drug interaction/metabolism studies have been requested from the applicant for ketoconazole, methadone, rifampicin, and efavirenz, as well as the evaluation of the combined SQV/RTV dosing regimen in subjects with hepatic impairment.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Given the extensive clinical experience with SQV, the evaluation of potential AEs for the proposed INV 500 mg FCT as presented in this NDA appears to be adequate. No new or unexpected AEs are evident from the data presented by the applicant.

The possible effects of gender on SQV exposure and AE profile are noted by the applicant. The evaluation as presented by the applicant in this NDA is noted. It is the opinion of the Clinical and Statistical Reviewers that these issues be addressed as postmarketing commitments (see Section 9.3).

### 7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data are adequate to support the review and approval of the INV 500 gm FCT. The non-QA/QC issues regarding AEs for the MaxCmin 1 appears to have been resolved following recoding with MedDRA. Although the SQV  $C_{min}$  data from the NR15720 study appears to be limited by the study investigators' assessment on patient compliance with study medications (see Section 7.1.5.6), in the opinion of this Medical Officer, this issue does not significantly affect the review of the data in support of this NDA.

### 7.2.9 Additional Submissions, Including Safety Update

Based on the data that were submitted at the time of initial NDA filing, a Safety Update was not formally submitted by the applicant nor was one requested by the Division. In August 2004, revised datasets that contained recoded AEs for MaxCmin 1 as well as relevant SAS programs for data analysis were provided to the Division by the applicant.

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The data provided in this NDA are consistent with the clinical experience with SQV in that GI-related AEs, such as nausea, vomiting, abdominal pain, and diarrhea, are the most frequently reported AEs with SQV use.

With respect to the possible relationship between AEs and SQV  $C_{min}$  levels, the data presented in this NDA do not show significant correlations. However, the interpretation of the data is limited by several factors, such as: 1) the once-daily SQV/RTV regimen that was used in NR15720, which has not formally been approved by the Agency; 2) whether or not study drug compliance may have affected the data; and 3) whether or not the assumption that Week 4  $C_{min}$  levels are indicative of SQV trough levels throughout the duration of the study.

With respect to the relationship between gender and AEs, data from the MaxCmin 1 PK substudy indicate that there is a trend towards females reporting more AEs (all causes and possibly GI-related) at a shorter time period from the start of SQV/RTV administration as compared to male subjects. This interpretation is complicated by a number of factors including the heterogeneous nature of the study population, limited number of female participants, higher proportion of females who were treatment-naïve/PI-naïve as compared to males, and possible confounding effects of concomitant meds and lack of assessments for patient compliance. In the context of these limitations and the fact that no new and unexpected AEs were noted during the safety review for this NDA, no labeling changes are proposed at this time. However, the applicant will be asked to further study the possible effects of SQV exposure and gender on the AE profile of SQV/RTV dosing regimen (Section 9.2.3).

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The applicant pooled safety data from two PK studies in which healthy volunteers were given RTV run-in for 14 days and then received alternating single doses of INV FCT or INV HGCG with RTV. In the opinion of this Medical Officer, this pooling is appropriate given that the same study drug regimen was used in the two studies and the small number (20) of volunteers in one of the studies.

Neither the applicant nor the Clinical/Statistical Review team pooled results from studies NR15720 and MaxCmin 1. This was due to a number of factors, including: once daily vs. BID RTV boosted regimens likely to yield different PK (higher  $C_{max}$ , lower  $C_{min}$  anticipated in general) due to different dosing regimens and different study entry/exclusion criteria and demographics (see Appendix for additional details).

#### 7.4.1.1 Pooled data vs. individual study data

Given the limited scope of these two healthy volunteer PK studies that were pooled for safety analysis, no comparison was performed to evaluate the pooled data vs. those of individual studies.

#### 7.4.1.2 Combining data

Given the scope of the two healthy volunteer studies, pooling of the data without formal weighting procedures is deemed acceptable by the Medical and Statistical Reviewers.

### 7.4.2 Explorations for Predictive Factors

Given the data presented in this NDA, explorations for possible relationships between AE profile of SQV and SQV exposure as well as with gender are deemed acceptable and appropriate by this Medical Officer. The applicant will be asked to further study these issues as postmarketing commitments.

#### 7.4.2.1 Explorations for dose dependency for adverse findings

Please see the Integrated Safety Review.

#### 7.4.2.2 Explorations for time dependency for adverse findings

Please see the Integrated Safety Review.

#### 7.4.2.3 Explorations for drug-demographic interactions

Please see the Integrated Safety Review.

#### 7.4.2.4 Explorations for drug-disease interactions

These exploratory analyses were not performed by the applicant. Given the nature of data presented in this NDA as well as the previous clinical experience with SQV, this is acceptable in the opinion of this Medical Officer.

#### 7.4.2.5 Explorations for drug-drug interactions

No new drug interaction studies are included in this NDA. It should be noted that postmarketing commitments from the December 2003 approval of SQV/RTV 1000 mg/100 mg regimen included a number of drug interaction studies with the new twice daily regimen.

#### 7.4.3 Causality Determination

Based on the data and clinical narratives presented in this NDA, in the opinion of this Medical Officer, the causality determinations for the safety analysis are deemed to be acceptable.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The recommended dosing regimen for INV FCT is 1000 mg /100 mg RTV BID, which is identical to that approved in December 2003 for INV HGC and FTV. The PK studies in this NDA support the notion that the SQV exposure following dosing of INV FCT at 1000 mg BID with RTV 100 mg BID will be similar to that generated by RTV-boosted dosing of FTV and INV HGC.

### 8.2 Drug-Drug Interactions

Drug interactions with SQV were most recently reviewed in December 2003 for the approval of 1000 mg FTV or INV HGC/100 mg RTV BID dosing regimen. As postmarketing commitments, the applicant is in the process of fulfilling drug interaction studies of SQV/RTV 1000 mg/100 mg BID with efavirenz, ketoconazole, methadone, and rifampicin. No new drug interactions involving SQV are presented in this NDA. Please see Dr. DiGiacinto's ClinPharm Review for additional details.

### **8.3 Special Populations**

In this NDA, no new dosing considerations for special populations are included. Please see Sections 8.2 and 8.4 for additional details on further studies in patients with hepatic impairment and pediatric patients.

### **8.4 Pediatrics**

The pediatric Written Request for SQV has been resubmitted in November 2004. Study reports for the fulfillment of this Written Request are to be submitted to the Agency on or before March 31, 2006.

### **8.5 Advisory Committee Meeting**

During the course of the review process, this NDA was not discussed in an Advisory Committee meeting.

### **8.6 Literature Review**

The recent publication by Fletcher, et al. (2004) is relevant to this NDA since the paper discusses gender effects of SQV exposure (please see Section 2.5).

### **8.7 Postmarketing Risk Management Plan**

In this NDA, the applicant has not included a formal Postmarketing Risk Management plan. Please see Section 9.3 for postmarketing commitments that are requested by the Agency.

### **8.8 Other Relevant Materials**

The Office of Drug Safety consultative report on the AEs reported with SQV/RTV combination regimens has been included in the December 2003 NDA Clinical Review. The relevant sections of the ODS reports have been summarized above in Section 7.1.17.

## **9 OVERALL ASSESSMENT**

### **9.1 Conclusions**

The three PK studies in healthy volunteers were reviewed for safety. Data from BP15058 and BP15359, in which subjects received RTV-boosted SQV, were pooled by the applicant for this review. The AE profile of SQV as demonstrated in these three studies was consistent with those previously associated with SQV and/or RTV use.

In the two studies in HIV-infected patients, the safety profile of subjects who received SQV/RTV were also reviewed for safety with specific emphasis on the possible effects of SQV

$C_{min}$  and gender. It should be noted that the MaxCmin 1 study was reviewed in December 2003 for safety and efficacy. For this review process, revised datasets from this study bearing MedDRA coded AEs were re-analyzed by the Clinical and Statistical Reviewers. For both studies, Week 4 SQV  $C_{min}$  levels were provided for a subset of subjects.

In the NR15720 study, male and female subjects in the pharmacokinetic substudy had similar Week 4 SQV  $C_{min}$  levels and also had similar adverse event profiles. In the MaxCmin 1 study, the mean SQV  $C_{min}$  level for female subjects ( $n = 15$ ) was approximately 1.6 fold than that for male subjects ( $n = 54$ ). Moreover, in the MaxCmin 1 study, female subjects reported a higher median number of adverse events (all body systems and those involving the gastrointestinal system) and in general, experienced a shorter time to onset of such adverse events as compared to male subjects. However, the applicant states that there was no obvious correlation between Week 4 SQV  $C_{min}$  levels and the frequency, type, and/or intensity of adverse events. With regard to laboratory parameters, in both studies, the applicant notes that there was no evidence that increased SQV  $C_{min}$  levels were correlated with organ system function, including hepatic function.

In general, these findings were confirmed by the Clinical and Statistical Reviewers. However, a several limitations of the pharmacokinetic substudies, such as the relatively small number of female subjects, the use of FTV, and the heterogeneous nature of the patient population with respect to baseline factors (e.g. history of antiretroviral treatment), are noted by the Reviewers. Thus, at this time, no formal changes in the product label are requested regarding possible gender effects on SQV exposure and safety profile; the applicant will be asked to address these issues in greater detail as postmarketing commitments.

## **9.2 Recommendation on Regulatory Action**

Based on the review of this NDA, it is the collective opinion of the Clinical and Statistical Reviewers that the INV 500 mg FCT should be approved. No significant deficiencies that preclude the approval of this NDA are identified. Based on its pharmacokinetic properties, INV FCT is expected to have an efficacy profile that is similar to that of INV HGC. The benefit of decreased pill burden to improve tolerability and compliance to antiretroviral treatment outweigh the risks of SQV-associated adverse events; based on this notion, this NDA was considered under a Priority Review. At this time, no formal changes in the product label are requested regarding possible gender effects on SQV exposure and safety profile; the applicant will be asked to address these issues in greater detail as postmarketing commitments.

## **9.3 Recommendation on Postmarketing Actions**

### **9.3.1 Risk Management Activity**

Please see the following section for postmarketing commitments. At this time, given the available data, no other risk management activities specific to the proposed INV 500 mg FCT are requested.

### 9.3.2 Required Phase 4 Commitments

Based on the review of data in this NDA, the following postmarketing commitments are requested by the Division:

- Conduct a retrospective analysis on the effects of gender on the safety profile of SQV 1000 mg /RTV 100 mg. Safety data should be provided from at least 50-100 female participants with appropriately matched comparative data from male subjects.
- Conduct a safety analysis by gender and saquinavir levels for subjects who received SQV 1000 mg/RTV 100 mg and were enrolled in the pharmacokinetic substudies of the MaxCmin 1 and MaxCmin 2 studies. Data from the two studies should be pooled for analysis and a uniform adverse event coding system should be used.
- Determine the baseline genotype of all PI-experienced responders in the MaxCmin 1 and MaxCmin 2 studies and submit in the resistance template format. Resubmit MaxCmin 1 and MaxCmin 2 failure dataset with a column identifying isolate (specifically “baseline”) and with a column identifying outcome (nonresponder, rebound, censored, etc.)

The Final Study reports for the first two postmarketing commitments are to be forwarded to the Agency within 12 months of the action date for this NDA. The Final Report for the third postmarketing commitment is to be forwarded to the Agency within six months of the action date for this NDA.

### 9.3.3 Other Phase 4 Requests

As of this writing, no other Phase 4 commitments are requested by the Agency.

## 9.4 Labeling Review

The following are the major revisions (insertions as underlined, deletions as struck-out text) that are requested in the applicant’s proposed package insert:

### **Description:**

INVIRASE is also available as a light orange to greyish- or brownish-orange, oval cylindrical, biconvex film coated tablet for oral administration in a 500-mg strength (as saquinavir free base). Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, povidone K30, croscarmellose sodium, and magnesium stearate. Each film coat contains hypromellose, titanium dioxide, talc, iron oxide yellow, iron oxide red, and triacetin.

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

BP17653: Bioavailability of 500 mg saquinavir mesylate tablet relative to INVIRASE® 200 mg capsule after the administration of a single oral dose of 1000 mg under fed conditions.

Study Design and Objective: The objective of this study was to determine the bioavailability of the INV 500 mg FCT relative to the INV 200 mg HGC after a single oral dose of 1000 mg SQV administered with food.

This was a Phase I, single-center, open-label, randomized, two-treatment, two-sequence, four-period, replicated crossover study with a washout of two days between the administrations of SQV. Each subject was randomized to receive one of two treatment sequences (ABAB or BABA, where A: INV HGC 200 mg and B: INV 500 mg FCT). This study was conducted at the Roche Clinical Pharmacology Unit, Welwyn Garden City, Hertfordshire, UK.

Major inclusion criteria were: male or non-pregnant female volunteer of any race; aged 18-65 inclusive; female volunteers had to be of non-childbearing potential or under efficient contraception; BMI of 18-30 inclusive; non-tobacco user and non-patch user; and able to participate in the study and to give informed consent.

Major exclusion criteria were: history of clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, cardiovascular, endocrinological, or allergic disease; any major illness within one month prior to screening; no recent herbal supplements or medications, including CYP3A4 inhibitors or inducers (except for aspirin or paracetamol up to 48 hours before dosing and oral contraceptive pills and hormone replacement therapy, which were allowed throughout the study); clinically significant allergic reactions or abnormal laboratory tests; or participation in a clinical study with an investigational drug within three months prior to start of dosing; seropositive for HIV, HBV, or HCV, recent blood loss or donation, and history of and/or active alcohol and/or drug abuse. From 14 day prior to SQV dosing and throughout the administration periods, subjects were not permitted to consume grapefruit or to drink grapefruit juice or alcohol.

Subjects received a single dose of SQV 1000 mg (dosed as INV HGC or INV FCT) following a standard high fat breakfast on the morning of days 1, 4, 7, and 10 following an overnight fast of at least ten hours. Subjects were confined to the study center from the evenings of days -1, 3, 6, and 9 until the completion of post-dose blood collections at various intervals up to 24 hours post-dose. A follow-up visit was performed 15-21 days following the last dose. Clinical laboratory tests (including hematology, serum chemistries including LFTs, and urinalysis) as well as vital signs were obtained at screening, prior to dosing on Days 1, 4, 7, and 10, and at the follow-up visit. A 12-lead ECG was obtained at screening, pre-dose on Days 1 and 10, and at follow-up.

A total of twenty (ten male and ten female) subjects were enrolled into and received all scheduled doses of INV FCT (2 x 500 mg) and INV HGC (5 x 200 mg) as specified in the

protocol. All were Caucasian with a mean age of 43.2 years, mean weight of 69.5 kg, and a mean BMI of 24.3 (range: 19.1 – 29.9). There were no marked differences in the demographic characteristics between female and male subjects in this study.

**Pharmacokinetics:** Please see the ClinPharm review for a detailed review of the pharmacokinetic results from this study. The following pharmacokinetic parameters for SQV were collected:  $AUC_{0-\infty}$ ,  $AUC_{0-last}$ ,  $C_{max}$ ,  $t_{max}$ ,  $t_{1/2\beta}$ , and  $CL/F$ . In brief, following the administration of SQV in either of the two formulations, the pharmacokinetics of SQV were comparable with the possible exception of higher  $AUC_{0-\infty}$  for INV 500 mg FCT as compared with INV HGC among the female subjects in the study. In females, the mean estimated SQV exposure ratio after INV FCT vs. that following INV HGC was approximately 1.37 (90% CI: 1.17-1.59) while in male subjects, the corresponding ratio of  $AUC_{0-\infty}$  was 0.99 (90% CI: 0.85-1.15). With respect to  $C_{max}$  for SQV, the applicant did not observe gender-related effects.

**Safety:** No deaths, SAEs, or premature study withdrawals due to AEs were noted during the study. For analysis of AEs that occurred following drug administration, the following definitions for AE reporting time windows were used:

- INV HGC period: Time period from the first administration of INV HGC until the subsequent administration of INV FCT (approximately 72 hours). For reporting purposes, the two INV HGC administration periods were combined since subjects received INV HGC twice during the study.
- INV FCT period: Time period from the first administration of INV FCT until the subsequent Administration of INV HGC (approximately 72 hours). For reporting purposes, the two INV FCT administration periods were combined since subjects received INV FCT twice during the study.

A total of 17 subjects (85%) reported a total of 38 AEs following INV FCT dosing and 14 subjects (70%) reported 25 AEs following INV HGC administration (Table 28). The most commonly reported AE was venipuncture site bruise (10 subjects (50%) vs. seven subjects (35%) in the FCT and HGC periods, respectively). Slightly higher occurrence of gastrointestinal AEs was noted during the INV FCT administration periods as compared with during the INV HGC period. In the opinion of this Medical Officer, the clinical significance of this observation in this study is limited because of non-RTV boosted INV administration in a small-scale Phase I study.

Table 28. Summary of All AEs by Body System and Trial Treatment: Study BP17653.

Body System/AE	All Periods INV FCT 1000 mg po N = 20 # (%)	All Periods INV HGC 1000 mg po N = 20 # (%)
<b>All Body Systems</b>		
Total # with ≥ 1 AE	17 (85%)	14 (70%)
Total # of AEs	38	25
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>		
Total # with ≥ 1 AE	11 (55%)	7 (35%)

Venipuncture Site Bruise	10 (50%)	7 (35%)
Cannula Site Reaction	3 (15%)	1 (5%)
Total Number of AEs	13	8
<b>NERVOUS SYSTEM DISORDERS</b>		
Total # with $\geq$ 1 AE	5 (25%)	6 (30%)
Headache	5 (25%)	6 (30%)
Dizziness	1 (5%)	1 (5%)
Total Number of AEs	6	7
<b>GASTROINTESTINAL DISORDERS</b>		
Total # with $\geq$ 1 AE	5 (25%)	3 (15%)
Abdominal Pain	3 (15%)	-
Loose Stools	2 (10%)	1 (5%)
Nausea	2 (10%)	1 (5%)
Infrequent Bowel Movements	-	1 (5%)
Toothache	1 (5%)	-
Total Number of AEs	8	3

Source: NDA 21,785, Module 5, Vol. 12, pp. 44-5.

The majority of AEs were deemed to be unrelated to study treatment. Three subjects reported AEs (headache, loose stools/abdominal pain/headache/nausea, and dysphoria) deemed remotely related to treatment during the INV FCT administration periods. Four subjects reported AEs (headache x 2, headache/loose stools, and headache/dizziness) deemed remotely related to treatment during the INV HGC administration periods. The majority of AEs were mild in intensity while four subjects reported five AEs (cough, cystitis, headache, ear infection, and headache) deemed moderate in severity.

Please see the Integrated Safety Review (Section 7) for analysis of laboratory values, vital signs, and ECG readings.

BP17058: Assessment of the bioavailability of the 500 mg SQV mesylate tablet combined with RTV relative to INV 200 mg capsule with RTV.

Study Design and Objective: The objective of this study was to determine the bioavailability of the INV 500 mg FCT combined with RTV relative to INV 200 mg HGC with RTV.

This was a Phase 1, single-center, open-label, randomized, four-period, two-treatment, replicated crossover study with a washout of two days between SQV administrations. Each subject was randomized to one of two SQV administration sequences (ABAB or BABA where A: INV HGC and B: INV FCT). The study was designed to enroll 20 healthy adult male volunteers in a single center in Strasbourg, France.

Major inclusion criteria were: male volunteer of any race; aged 18-65 inclusive; BMI of 18-30 inclusive; non-tobacco user; and able to participate in the study and to give informed consent.

Major exclusion criteria were: history of clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, cardiovascular, endocrinological, or allergic disease; any major illness within one month prior to screening; no recent herbal supplements or medications,

including CYP3A4 inhibitors or inducers (except for aspirin or paracetamol up to 48 hours before dosing); clinically significant allergic reactions or abnormal laboratory tests; participation in a clinical study with an investigational drug within three months prior to start of dosing; seropositive for HIV, HBV, or HCV, recent blood loss or donation, and history of and/or active alcohol and/or drug abuse. From 14 day prior to RTV dosing and throughout the RTV administration periods, subjects were not permitted to consume grapefruit or to drink grapefruit juice or alcohol.

Subjects received RTV 100 mg BID for 24 days and were confined to the study center from the evening of days 13, 16, 19, and 22. On the mornings of days 14, 17, 20, and 23, after an overnight fast of  $\geq 10$  hours, subjects received a single dose of 1000 mg INV as FCT or HGC with the morning RTV dose within five minutes after the completion of a standard high fat breakfast. Thereafter, subjects underwent pharmacokinetic monitoring and safety assessments including clinical laboratory tests, vital signs, and 12-lead ECGs. A follow-up visit was performed 15-21 days after the last dose. A follow-up visit was performed 15-21 days following the last dose. Subjects underwent full clinical laboratory tests (including hematology, serum chemistries with LFTs, and urinalysis) in the fasted state at screening, and on Days 1, 8, and 17 before RTV dosing and at follow-up. On Days 14, 20, and 23, a reduced set of clinical laboratory tests (including serum chemistries with LFTs and urinalysis) were obtained before breakfast. Vital signs were measured at screening, on Days 1, 8, 14, 17, 20, 23, and at follow-up. ECGs (12-lead) were obtained at screening, on Days 8, 17, and at follow-up.

A total of 20 healthy male subjects aged 18-65 years enrolled into the study. The demographic characteristics of the study participants are summarized in Table 29 (see 10.1.3 below, under study 17359). Four participants withdrew prematurely: one due to diarrhea/vomiting on Day 9 of RTV treatment, another for personal reasons/consent withdrawal, and two due to refusal to eat or complete the breakfast after Days 13 and 20 of the study, respectively. Of the 16 that completed the study, seven were randomized to the treatment sequence ABAB and nine were assigned to treatment sequence BABA. The applicant notes that occasional deviations from the protocol-defined standard high-fat breakfast were noted. Such deviations were no more than  $\pm 10\%$  with respect to the caloric content and no more than  $+16\%$  with regard to the fat content.

Pharmacokinetics: Please refer to Dr. DiGiacinto's ClinPharm review for an extensive review of the pharmacokinetic results from this study. In brief, the applicant states that the INV 500 mg FCT exhibited similar bioavailability to the INV 200 mg HGC when taken in combination with 100 mg RTV. The mean exposure ratio of FCT vs. HGC was 1.05 (90% CI: 0.94-1.18) for  $AUC_{0-\infty}$  and 1.13 (90% CI: 1.00-1.26) for  $C_{max}$  of SQV. For  $AUC_{0-\infty}$  and  $C_{max}$  of SQV, the CV of inter-subject variability ranged from 46% to 58% and that for the intrasubject variability was less than 25%. Because of the irregularities in the supplied food and preparation, the breakfast that was served on the SQV dosing days was not standard (as defined in the protocol) in all instances. According to the applicant's analysis, the different contents of the breakfast did not affect the  $AUC_{0-\infty}$  or  $C_{max}$  of SQV.

Safety: The AEs from this study were pooled by the applicant with those from BP17359. Such pooled data analysis is summarized in Section 7.1.5.3.

Please see the Integrated Safety Review (Section 7) for analysis of laboratory values, vital signs, and ECG readings.

BP17359: A bioequivalence study comparing 500 mg SQV mesylate tablets with INVIRASE 200 mg capsules administered under fed conditions, at a single oral dose of 1000 mg and combined with ritonavir 100 mg capsules BID.

Study Design and Objective: The objective of this study was to establish the bioequivalence of the 500 mg INV FCT to the INV 200 mg HGC. Both treatments were administered under fed conditions and combined with RTV capsules 100 mg BID.

This was a Phase 1, two center, open-label, randomized, two-sequence, four-period, two-treatment, replicated crossover study with a washout of two days between administration of SQV. Each subject was randomized to receive one of two SQV treatment sequences: ABAB or BABA (where A: INV HGC + RTV and B: INV FCT + RTV). The study was designed to enroll a total of 100 healthy adult female or male volunteers at two centers in England. Male subjects were recruited at both sites while females were recruited at one of the two sites.

Major inclusion criteria were: male or non-pregnant female volunteer of any race; aged 18-65 inclusive; female volunteers had to be of non-childbearing potential or under efficient contraception; BMI of 18-30 inclusive; non-tobacco user and non-patch user; and able to participate in the study and to give informed consent. Due to drug interactions with RTV, contraceptive methods based on estrogens/progestogens were not permitted during this study.

Major exclusion criteria were: history of clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, cardiovascular, endocrinological, or allergic disease; any major illness within one month prior to screening; no recent herbal supplements or medications, including CYP3A4 inhibitors or inducers (except for aspirin or paracetamol up to 48 hours before dosing); clinically significant allergic reactions or abnormal laboratory tests; or participation in a clinical study with an investigational drug within three months prior to start of dosing; seropositive for HIV, HBV, or HCV, recent blood loss or donation, and history of and/or active alcohol and/or drug abuse. From 14 days prior to SQV dosing and throughout the administration periods, subjects were not permitted to consume grapefruit or to drink grapefruit juice or alcohol.

The criteria for pharmacokinetics and safety monitoring were essentially identical to those for study BP17058 (summarized above in Section 10.1.2). Subjects received RTV 100 mg BID for 24 days and were confined to the study center from the evening of Days 13, 16, 19, and 22. On the mornings of Days 14, 17, 20, and 23, after an overnight fast of  $\geq 10$  hours, subjects received a single dose of 1000 mg INV as FCT or HGC with the morning RTV dose within five minutes after the completion of a standard high fat breakfast. Thereafter, subjects underwent pharmacokinetic monitoring and safety assessments including clinical laboratory tests, vital signs, and 12-lead ECGs. A follow-up visit was performed 15-21 days following the last dose. Subjects underwent full clinical laboratory tests (including hematology, serum chemistries with

LFTs, and urinalysis) in the fasted state at screening, and on Days 1, 8, and 17 before RTV dosing and at follow-up. On Days 14, 20, and 23, a reduced set of clinical laboratory tests (including serum chemistries with LFTs and urinalysis) were obtained before breakfast. A urine pregnancy test was performed at screening, pre-dose on Days 1, 14, and 23, and at follow-up. Vital signs were measured at screening, on Days 1, 8, 14, 17, 20, 23, and at follow-up. ECGs (12-lead) were obtained at screening, on Days 8, 17, and at follow-up.

A total of 100 (93 male and seven female) healthy subjects were enrolled into the study. A total of six male participants withdrew prematurely from the study. Four were due to AEs prior to Day 14 and during the RTV run-in period, one was due to an AE on Day 14 after the first dose of SQV, and one was due to withdrawal of consent on Day 2. The study design and dosing schedules were essentially identical to those for BP17058. However, in this study, the applicant reported no irregularities related with study meals.

The demographics of the study participants in studies BP17058 and BP17359 are summarized in the following table:

Table 29. Summary of Demographic Characteristics of Healthy Volunteers.

Variable	BP17653 Bioavailability N = 20	BP17058/BP17359 Bioavailability/Bioequivalence N = 120
<b>Gender</b>		
Male	10 (50%)	113 (94%)
Female	10 (50%)	7 (6%)
<b>Race</b>		
Caucasian	20 (100%)	114 (95%)
Black	-	2 (2%)
Oriental	-	-
Other	-	4 (3%)
<b>Age</b>		
Mean ± SD	43.2 ± 11.6	35.4 ± 12.4
Median	44.0	32.0
Min-Max	20 – 64	19 – 65
<b>BMI (kg/m<sup>2</sup>)</b>		
Mean ± SD	24.3 ± 3.6	25.0 ± 2.5
Median	23.7	25.0
Min-Max	19.1 – 29.9	18.9 – 30.0
<b>Height (cm)</b>		
Mean ± SD	168.3	175.9
Median	165.5	176.0
Min-Max	152 – 186	156 – 193
<b>Weight (kg)</b>		
Mean ± SD	69.5 ± 15.5	77.4 ± 9.8
Median	66.3	78.0
Min-Max	47.0 – 100.4	52.1 - 99.5

Source: NDA 21,785 Module 2, Vol. 1, p. 18.

**Pharmacokinetics:** For a detailed review of the pharmacokinetic results of this study, please refer to Dr. DiGiacinto's ClinPharm review. The applicant states that RTV-boosted dosing of INV FCT and INV HGC met the bioequivalence for both parameters,  $AUC_{0-\infty}$  and  $C_{max}$ . The applicant also notes that higher  $C_{max}$  values were detected when INV FCT/RTV was administered in the preceding period than when INV HGC/RTV was administered previously. The applicant states that this was considered an artifact and the bioequivalence conclusions of the study are deemed valid. Again, higher SQV exposure was noted in females; mean exposures in females were approximately 56% and 26% higher than in males with respect to  $AUC_{0-\infty}$  and  $C_{max}$ , respectively. Lastly, the applicant noted a difference in SQV exposure between the two study sites.

**Safety:** Please refer to Section 7.1.5.3. on the pooled safety data analysis. Please see the Integrated Safety Review (Section 7) for analysis of laboratory values, vital signs, and ECG readings.

#### NR15720

**Study Objectives:** The primary objective was to evaluate the virologic response to a combination of SQV (dosed as FTV) 1600 mg QD and RTV 100 mg QD, plus two NRTIs vs. efavirenz (EFV) 600 mg QD plus two NRTIs, with respect to the proportion of patients whose plasma HIV RNA level falls below the ultra-sensitive assay level of detection (50 copies/mL) at week 24 and at a follow-up extension at week 48.

The secondary objectives included: evaluation of the absolute change in HIV RNA; the proportion of patients whose viral HIV RNA levels reached < 400 copies/mL; change in CD4 and CD8 cell counts and CD4/CD8 ratio; the time to virologic response and virology response; safety; changes in fasting lipid levels and metabolic parameters; and pharmacokinetics.

**Study design:** This was a randomized, open-label, multi-center Phase 3B study to evaluate the efficacy and safety of SQV/RTV QD vs. that of EFV QD with two open-label, approved NRTIs (3TC, AZT, ddI, or d4T) for HIV-infected adults over 48 weeks. Subjects were randomly assigned 1: 1 to one of the two treatment groups: Arm A [SQV (FTV) 1600 mg QD + RTV 100 mg QD + two NRTIs] or Arm B [EFV 600 mg QD + two NRTIs].

With regard to treatment response, subjects were considered to be failing on treatment if they did not respond to the assigned therapy (virologic non-responders) or if they relapsed during study participation. Subjects were considered to be virologic non-responders if they experienced < 0.5 log reduction in plasma HIV RNA by 4 weeks of therapy, < 1.0 log reduction in plasma HIV RNA by 8 weeks of therapy, or an inability to sustain a 1.0 log reduction in plasma HIV RNA from week 8 to just prior to 24 weeks of therapy. Lastly, subjects were considered to have experienced virologic relapse if, despite having been compliant, had two consecutive HIV RNA levels  $\geq 1,000$  copies/mL  $\geq 10$  days apart following two consecutive HIV RNA values of < 50 copies/mL  $\geq 10$  days apart. According to the applicant, patients who discontinued therapy due to virological failure were not followed beyond the scheduled follow-ups.

If a subject experienced a grade 3 or 4 AE of laboratory abnormality that was considered possibly related to study drug, then the investigator was to discontinue all study drugs and follow the patient until the toxicity resolved to Grade 2 level. Following consultation with the Sponsor, the investigator may then resume study drugs at full doses or at a reduced dose, depending on the specific toxicity. Subjects who resumed a full or modified study drug regimen were to be followed weekly for two visits to monitor for recurrence of the toxicity. If the toxicity did not recur during such visits, the subject was to resume the regular study dosing and schedule. If the toxicity recurred, all drugs were to be discontinued. If the recurrent toxicity resolved within 4 weeks, then the dose modification process was to be repeated.

If a subject experienced an AE that was definitely related to the NRTI, then the investigator may change the offending NRTI to an alternative, approved NRTI at a QD or BID regimen and continue study medications. Such patients were monitored until the toxicity resolved to grade 2 level.

Major inclusion criteria were: HIV-seropositive male or non-pregnant/non-nursing female, age  $\geq$  18 years; HIV RNA  $\geq$  5,000 copies/mL (stratified as  $\geq$  5,000 – 75,000 vs.  $>$ 75,000 copies/mL) by the Roche Amplicor assay; CD4  $\geq$  75 cells/mm<sup>3</sup>; no previous treatment with antiretrovirals for  $\geq$  2 weeks; ability and willingness to provide appropriate consent and comply with study requirements; ability to tolerate the taste of RTV liquid formulation if RTV capsules were not available; and a negative pregnancy test within 14 days prior to study drug therapy (for female subjects of childbearing potential).

Major exclusion criteria were: female subjects who were lactating, pregnant, or of childbearing potential and not using two reliable, protocol-defined contraceptive methods; previous treatment with antiretrovirals for  $\geq$  2 weeks; Grade 3 or 4 laboratory or clinical abnormalities; laboratory abnormalities at screening (AST or ALT  $>$  3X ULN; bilirubin  $>$  2.5X ULN, amylase  $>$  2X ULN, WBC  $<$  1,000, hemoglobin  $<$  9.0 g/dL, platelet count  $<$  50,000 cels/mm<sup>3</sup>, or serum creatinine  $>$  2.5 mg/dL); acute or chronic hepatitis B or C; severe hepatic impairment; requirements for MAI bacteremia, CMV retinitis, tuberculosis, or toxoplasmosis maintenance therapy; unexplained chronic diarrhea ( $\geq$  5 bowel movements/day) or unexplained fever  $>$  38.5C x 14 days or more; malignancy (other than cutaneous Kaposi's sarcoma) requiring chemotherapy or radiotherapy; transfusion dependence; receipt of an investigational new drug within 4 weeks prior to screening; history of psychological illness or condition that may have affected comprehension of study requirements; active substance abuse; hypersensitivity to any of the prescribed antiretroviral drugs or to any component of such drugs; and use of drugs contraindicated with the antiretroviral drugs used in this study.

Patients were screened two weeks prior to the baseline visit and initiation of study drug treatment. At screening, laboratory safety tests, including hepatitis B and C testing, hematology, fasting chemistry profile (including LFTs), urinalysis, and pregnancy test were obtained and HIV RNA levels and CD4 cell counts were measured. At the baseline visit, subjects underwent a medical history evaluation, complete physical examination, laboratory safety tests including hematology, fasting chemistry panel and lipid profile, HIV RNA level and CD4 cell counts.

Thereafter, subjects were seen at Weeks 4, 8, 12, 16, 20, 24, 32, 40, and 48. At these visits, subjects underwent measurement of HIV RNA levels, CD4 cell counts, hematology, and fasting chemistries (including LFTs). Fasting lipid profiles were obtained from subjects at Weeks 12, 24, 48, and if needed, at Weeks 72 and 84 and study closure. Patients who continued with treatment beyond Week 48 were also seen at Weeks 60, 72, and 84 as well as at study closure. In each treatment arm, a subset of subjects was to undergo anthropomorphic measurements but due to difficulty obtaining the requisite measurements at study sites, these data are not described in the Final Study Report. Patients who discontinued study drug for any reason were also seen for the scheduled study assessments. All visits were to take place within a two-week window of the scheduled date.

At every visit, subjects were assessed for AEs, which were graded as mild, moderate, severe, or life-threatening (grades 1-4, respectively). The investigator also evaluated the relation of each AE to the study medication regimen as unrelated, possible, or probable. All AEs were followed until resolution or adequate explanation, even after cessation of study medication. AEs were coded using MedDRA version 1.5.

**Results:** The safety data from the NR15720 study were submitted by the applicant in support of this NDA for the proposed INV 500 mg FCT formulation. The applicant has not supported safety or efficacy data from this study in support of a once-daily SQV dosing regimen. Thus, only the safety data from subjects in the once daily SQV/RTV arm are reviewed in support of this NDA. No efficacy data from this study were reviewed.

In all, 269 potential subjects were screened and 171 (Arm A: FTV/RTV, N = 86; Arm B: EFV, N = 85) were randomized into the study. Arm A had 75 subjects in the primary ITT population (including all patients who received active study drug after randomization and who had at least one on-drug efficacy evaluation), 81 in the safety population (including all randomized patients who received at least one dose of study drug and had at least one post-baseline safety evaluation), and 51 subjects who completed the 48 week study. In Arm A, of the 75 in the PITT group, eight prematurely discontinued from the study due to AEs; one due to insufficient therapeutic response, eight due to failure to return for follow-up, and 11 due to refused treatment/did not cooperate/consent withdrawal. There were five patients in all who discontinued from their original randomized arm, switched to the alternate treatment arm, and agreed to be followed according to the scheduled visits. Patient 2149 was originally assigned to the FTV/RTV arm, and patients 1041, 1086, 1091, and 2091 were originally assigned to the EFV arm. For these patients, data collected before the switch date were included in the safety analysis.

**Demographics:** In the PITT population of Arm A, there were 53 (71%) male participants and the mean age was 37.2 years (median 36, range: 20 – 61). The mean weight was 78 kg and the mean height was 173.5 cm. The racial composition of this study group was as follows: black: 34 (45%), Caucasian/white: 28 (37%), Hispanic: 7 (9%), and other: 7 (9%). The baseline HIV RNA level (mean  $\pm$  S.D.) was  $4.79 \pm 0.60$  log<sub>10</sub> copies/mL (IQR: 4.40, 5.22) and the baseline CD4 cell count (mean  $\pm$  S.D.) was  $372 \pm 190$  cells/mm<sup>3</sup> (IQR: 243, 483). Of the participants in Arm A, 39 (52%) had pre-baseline HIV RNA levels  $\geq 5,000 - 75,000$  copies/mL and 36 (48%) had  $>75,000$

copies/mL. The demographics data for the NR15720 and the MaxCmin 1 studies are shown in Table 30.

Table 30. Summary of Demographic Characteristics of HIV Patients in Study NR15720 and Study MaxCmin 1 Who Received SQV.

Variable	NR15720 (Primary ITT Population) N = 75	MaxCmin 1 N = 148
<b>Gender</b>		
Male	53 (71%)	122 (82%)
Female	22 (29%)	26 (18%)
<b>Race</b>		
Caucasian	28 (37%)	127 (86%)
Black	34 (45%)	14 (9%)
Hispanic	6 (8%)	-
Other	7 (9%)	7 (5%)
<b>Age</b>		
Mean ± SD	37.2 ± 9.7	41.4 ± 9.6
Median	36.0	39.0
Min-Max	20 – 61	19 – 71
<b>BMI (kg/m<sup>2</sup>)</b>		
Mean ± SD	24.3 ± 3.6	23.4 ± 3.5
Median	23.7	23.1
Min-Max	19.1 – 29.9	16 – 35
<b>Height (cm)</b>		
Mean ± SD	173.5 ± 8.3	173.9 ± 8.9
Median	174.0	174.0
Min-Max	157 – 190	153 – 205
<b>Weight (kg)</b>		
Mean ± SD	78.0 ± 16.5	71.0 ± 12.1
Median	75.0	71.5
Min-Max	52.0 – 126.0	41 – 108

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Source: NDA 21,785, Module 2, Vol. 1, p. 19.

A subset of subjects (n = 60) participated in the PK substudy in which SQV C<sub>min</sub> levels were measured after four weeks of study drug treatment. The demographics of such PK substudy participants in NR15720 and the MaxCmin 1 studies are shown in Table 31.

Table 31. Summary of Demographic Characteristics of HIV Patients in the Pharmacokinetic Sub-studies in NR15720 and MaxCmin 1.

Variable	NR15720 All PK Patients N = 60	MaxCmin 1 All PK Patients N = 69
<b>Gender</b>		
Male	42 (70%)	54 (78%)
Female	18 (30%)	15 (22%)
<b>Race</b>		
Caucasian	21 (35%)	62 (90%)
Black	27 (45%)	4 (6%)
Other	12 (20%)	3 (4%)

<b>Age</b>		
Mean ± SD	38.3 ± 10.0	40.8 ± 9.4
Median	36.0	39.0
Min-Max	22 – 62	19 – 60
<b>BMI (kg/m<sup>2</sup>)</b>		
Mean ± SD	-	23.5 ± 3.0
Median	-	23.1
Min-Max	-	16 – 32
<b>Height (cm)</b>		
Mean ± SD	173.6 ± 8.6	173.4 ± 8.7
Median	175.0	174.0
Min-Max	158 – 190	153 – 190
<b>Weight (kg)</b>		
Mean ± SD	79.6 ± 17.1	71.1 ± 11.7
Median	77.3	72.5
Min-Max	52 – 126	41 – 108
<b>HIV RNA at Screening (log<sub>10</sub> copies/mL)</b>		
Mean ± SD	4.8 ± 0.5	4.9 ± 0.9
Median	4.8	5.0
Min – Max	3.7 – 6.1	1.7 – 5.9

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Source: Adapted from NDA 21,785, Module 2, Vol. 1, p. 20.

Adjuvant NRTI treatment permitted in study NR15720 included ZDV, 3TC, ZDV/3TC, d4T, and ddI. All of these NRTIs were given as BID as described in the respective package inserts. The majority of patients (47 out of 75; 63%) received ZDV/3TC, and 27 subjects (36%) received 3TC/d4T. One subject received ZDV/ddI.

Safety: In Arm A, 71% of the subjects received study drug up to Week 24 (day 168; time window of Days 152 – 196) and 62% received study drug up to Week 48 (Day 336; time window of Day 308 – 377).

For additional safety data analyses, please see the Integrated Safety review (Section 7).

#### MaxCmin 1

This study has been extensively reviewed by Clinical and Statistical Reviewers in the Division in December 2003 (Murata, 2003; Zhou, 2003).

The MaxCmin 1 study was a Phase IV, randomized, open-label, parallel group, multi-center trial in which HIV-1 infected adult subjects were started on a BID regimen of either IDV (indinavir) and RTV at 800 mg and 100 mg respectively, or FTV and RTV at 1000 mg and 100 mg respectively. The total duration of treatment was 48 weeks. Prior to randomization to either of the PI arms, concomitant use of at least two NRTI/NNRTIs was decided by the treating physician for each patient. Provisions during the course of the study permitted switching of the SQV formulation from FTV to INV at the identical dose of 1000 mg BID with RTV.

The primary objective of this study was to determine whether there is equivalence in the incidence of virological failure for the IDV/RTV arm relative to the FTV/RTV arm. The secondary objectives included: determination of the differences in the CD4 lymphocyte count response; determination of the frequency of subjects with suppression of HIV RNA in the two treatment arms; assessment of the safety and tolerability of the two treatment arms; and determination of the plasma concentration of study drugs approximating the trough levels at weeks 4 and 48 after starting study medication.

Following a screening assessment performed up to four weeks prior to first dose of study drug, eligible patients were randomized into one of the two treatment arms. By clinical and laboratory monitoring at study Day 1 and at Weeks 4, 12, 24, 36, and 48, patients were assessed for safety, tolerability, and antiviral activity of the study medications. Such monitoring included vital signs, screening for adverse events, routine clinical laboratories, HIV RNA levels, and CD4+ cell count. In the study protocol, grading of adverse events as well as follow-up of such events are described.

Major inclusion criteria were:

- HIV-1 infected, male or non-pregnant female, > 18 years of age.
- Fulfillment of at least one of the following five criteria, provided that either (see following inclusion criterion) of the boosted PI-regimens studied in this trial was judged to be of benefit to the person:
  - Being PI-naïve.
  - Being PI-experienced and with a viral load  $\geq$  400 copies/ml.
  - Being PI-experienced and with a viral load  $\leq$  400 copies/ml and:
    - Experiencing adherence problems either before or currently on an ongoing mono-PI-containing regimen (irrespective of type and dosing schedule of the PI) AND/OR:
    - Currently experiencing toxicity to the PI-component of a mono-PI-containing regimen (other than IDV or SQV) AND/OR:
    - Experiencing typical RTV-associated adverse events on a RTV (at doses no less than 300 mg BID) boosted double-PI containing regimen (regardless of type and dosing schedule of other PI). Prior exposure to any of the three PIs used in the study did not preclude enrollment.

As evident from the inclusion criteria, the MaxCmin 1 study was intended to determine the safety and efficacy of FTV/RTV in a heterogeneous population of HIV-infected patients. With respect to antiretroviral therapy, the study patients may be treatment-naïve or treatment-experienced with PIs. If in the latter group, the viral load in these patients may or may not be suppressed below 400 copies/mL, and with or without adverse events/tolerability issues.

The major exclusion criteria were:

- Subjects whom in the investigator's opinion were unlikely to complete the 48 week trial period.

Clinical/Statistical Review

Yoshihiko Murata, M.D., Ph.D., Susan Zhou, Ph.D.

NDA 21785, N-000

INVIRASE® (saquinavir mesylate) 500 mg film-coated tablets

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- Subjects with current alcohol or illicit drug use which, in the opinion of the investigator, may interfere with the subjects' ability to comply with the dosing schedule and protocol evaluations.
- Subjects on concomitant medications which—in the opinion of the investigator and according to drug product labeling—would result in clinically significant interactions with any of the PIs assessed in this trial.
- Subjects being pregnant or breast feeding.
- Subjects with renal failure requiring dialysis.
- Subjects suffering from a serious medical condition, including one or more AIDS defining events, which in the opinion of the investigator, would compromise the safety of the subject.

In all, 317 subjects were randomized to one of two treatment arms: IDV/RTV (159 subjects) or FTV/RTV (158 subjects). Following randomization, 11 participants (10 in FTV/RTV arm and 1 in IDV/RTV arm) did not start scheduled randomized treatment. Please refer to the December, 2003 Clinical and Statistical Reviews of NDA 20628/20828 for a complete discussion of the Results of the MaxCmin 1 study, including subject disposition, demographics, baseline characteristics, efficacy, and safety. For this NDA, it should be noted that 69 out of 148 patients in this study arm underwent PK sampling at Week 4 and thus had extrapolated SQV plasma trough ( $C_{min}$ ) values calculated.

The demographics of subjects in the FTV/RTV arm of this study as well as those in the PK substudy are shown in Tables 30 and 31 under the NR15720 study summary (Section 10.1.4). The following table summarizes antiretroviral drugs that subjects took with the study medications.

Table 32. Adjuvant Antiretroviral Therapy in the MaxCmin 1 Study.

Drug Combination	SQV/RTV N = 148
ZDV + 3TC	83 (56%)
ZDV + ddI	5 (3%)
d4T + ddI	11 (7%)
d4T + 3TC	31 (21%)
ZDV + 3TC + ABC	1 (1%)
Other Combinations <sup>a</sup>	11 (7%)
Only 1 NRTI	4 (3%)
No NRTIs	2 (1%)
NNRTI	7 (5%)

a: Other combinations included: ABC + 3TC (2); ABC + d4T (2); ABC + ddI (3); ddI + 3TC (1), ddC + ZDV (1); ABC + ddC + ddI (1); ddI + 3TC + d4T (1).

Source: Adapted from NDA 21,785, Module 2, Vol.1, p. 21.

For additional discussion of safety in the MaxCmin 1 study, please refer to Section 7, Integrated Review of Safety.

**Laboratory analysis:** At baseline and at subsequent study visits, blood was collected from each subject for the following laboratory analyses: hemoglobin, platelet count, WBC count, AST or ALT, total bilirubin, creatinine, serum amylase, total lymphocytes, HIV-1 RNA, and CD4+ lymphocyte count. Also, at baseline, and at weeks 4 and 48, fasting total and LDL cholesterol and fasting triglyceride levels were determined. These data have been formally reviewed by the Clinical and Statistical Reviews of MaxCmin 1 study data (Murata, 2003, and Zhou, 2003). For presentation of the relevant laboratory results and analyses, please refer to the Integrated Safety Review (Section 7):

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