Clinical Review of Supplemental Applications to NDA 20-628 and NDA 20-828

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Based on the data provided in the supplemental NDAs 20628 and 20828, it is recommended that the proposed combination twice-daily regimens of Fortovase® (FTV) 1000 mg with ritonavir (RTV) 100 mg and Invirase® (INV) 1000 mg with RTV 100 mg be approved. The proposed combination regimens offer the benefit of twice-daily dosing regimen instead of the previously approved thrice daily dosing schedules for both FTV and INV. The addition of low dose RTV to FTV or INV does not appear to significantly alter the adverse event profiles previously associated with use of INV and FTV. Addition of low dose RTV may subject patients taking the proposed combination regimens to adverse events associated with RTV. However, such risks are likely to be minimal and should be outweighed by the benefits of reduced pill burden and improved patient compliance to be anticipated from the twice daily dosing regimen.

Of note, the previously approved package insert for INV included the following: 1) FTV is the recommended formulation when saquinavir was to be used as part of an antiretroviral regimen, and 2) INV may be considered for use when combined with antiretroviral agents that significantly inhibited the metabolism of saquinavir. However, no recommendations on the dosing regimen for use with such metabolic inhibitors were given in the previous package insert. The data provided in these NDAs suggest that the twice daily dosing of INV with RTV at the proposed doses will significantly improve the patient exposure to saquinavir as compared to that expected from INV alone. Thus, the dosing of INV as 600 mg TID is no longer recommended for use.

The recommendation for approval of the proposed combination regimens is primarily based on the pharmacokinetic parameters of saquinavir following combination dosing of either FTV or INV formulations with RTV. In the EPIMED 1 study, in which SQV exposure generated by the proposed FTV/RTV and INV/RTV BID regimens were examined in HIV-infected adults, INV/RTV 1000 mg/100 mg BID was deemed not to be bioequivalent to FTV/RTV 1000 mg/100 mg BID. However, SQV exposures generated from both combination regimens were at least equivalent to that of the currently approved

FTV dosing regimen (1200 mg TID). Thus, both regimens are expected to achieve SQV exposure required to inhibit HIV replication.

In addition, the safety profile of FTV 1000 mg/ RTV 100 mg BID regimen over 48 weeks during the MaxCmin 1 study also supports the approval of the proposed combination regimens. Addition of low dose RTV did not significantly alter the adverse event profile of FTV. The safety analysis of the MaxCmin 1 study and review of post-marketing data revealed no new safety-related issues associated with combination dosing of FTV with RTV as compared to the previously described safety profile of FTV. With regard to efficacy, the suppression of HIV RNA levels associated with the proposed FTV/RTV 1000/100 mg BID regimen were comparable to that seen with use of another RTV-boosted protease inhibitor, indinavir. It should be noted that the comparator regimen is not approved for use in the treatment of HIV infection but is recommended a:

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Following the review of these two supplemental NDAs, several Phase 4 commitments were requested from the applicant. Most of such requests involve drug-drug interaction studies as well as pharmacokinetic studies of the proposed regimens in subjects with impaired hepatic function. The Division also asked the applicant to submit the final results of the MaxCmin 2 study in which the safety and efficacy profiles of the FTV/RTV combination regimen were compared to those of another combination regimen (lopinavir/RTV) in a heterogeneous population of HIV-infected patients. At the time of approval of the FTV/RTV combination regimen, the applicant was reminded of the outstanding Phase 4 commitments from previous approvals of FTV.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Trade (Generic) Names: Fortovase® (saquinavir); Invirase® (saquinavir mesylate).

Approved dosage forms: soft-gelatin capsules containing 200 mg saquinavir free base (Fortovase®); hard-gelatin capsules containing 200 mg saquinavir mesylate (Invirase®).

Currently approved dosing regimens: FTV: 1200 mg TID; INV: 600 mg TID.

Saquinavir (SQV), which functions as a protease inhibitor (PI) to block replication of the human immunodeficiency virus (HIV), was approved in 1995 as Invirase® (INV) hard-gelatin capsules and in 1997 as Fortovase® (FTV) soft-gelatin capsules. In these supplemental NDAs, the applicant seeks approval of twice-daily combination of FTV and INV with low doses of another protease inhibitor, ritonavir (RTV). In such combination regimens, SQV (from FTV or INV) is expected to function primarily as an inhibitor of

HIV-encoded protease while RTV functions as a pharmacological enhancer of SQV levels.

In these supplemental NDAs, the applicant provides 48 week safety and efficacy data from the MaxCmin 1 study. In this Phase IV, randomized, open-label, parallel group, multi-center trial study, 317 HIV-infected adults with varying treatment histories were randomized to receive either FTV/RTV 1000 mg/100 mg BID or another protease inhibitor (Indinavir®; IDV) 800 mg in combination with RTV 100 mg BID. The applicant also provides data from the EPIMED 1 study, in which SQV exposures following both proposed combination regimens were studied in 24 HIV-infected patients. The EPIMED 1 results were then used as a "pharmacokinetic bridge" to support the use of INV/RTV combination regimen based on the safety and efficacy of the previously approved FTV regimen and on the safety of the FTV/RTV regimen in the MaxCmin 1 study.

B. Efficacy

The efficacy of the proposed FTV/RTV regimen as shown in the MaxCmin 1 study was analyzed. In response to the Division's requests during the review of the NDAs, the applicant provided several efficacy analyses using the Division's time-to-loss-of-virologic-response algorithm. These analyses varied with respect to use of data from all study visits or protocol-scheduled visits, limits of quantitation for HIV RNA levels, and inclusion or exclusion of data from five patients whose HIV RNA levels were determined by a non-standard assay. Depending on the efficacy analysis, 52.9% – 63.3% of study subjects who received FTV/RTV achieved suppression (< 50 or < 400 copies/mL) of HIV RNA levels at 48 weeks. In general, the proportion of subjects in the FTV/RTV arm who achieved such suppression of HIV RNA levels was slightly greater than those in the comparator arm. The statistical significance of such differences varied slightly depending on the efficacy analysis ($p = 0.035 – 0.092$). Also, in general, in both arms of the MaxCmin 1 study, small and statistically non-significant (according to the applicant) increases in CD4+ cell counts were noted during the course of the study. As of this writing, the efficacy analyses of the applicant are being confirmed by Dr Susan Zhou, the Statistical Reviewer. Please refer to the statistical review for additional details, including efficacy subanalyses in special populations.

Of note, the comparator regimen of indinavir/RTV that was used in the MaxCmin 1 study has not been approved for treatment of HIV infection. A more rigorous test of efficacy of the proposed combination regimens would require the use of an approved RTV-boosted PI regimen such as lopinavir/RTV as the comparator regimen. Since the approval of the proposed combination regimens is primarily based on pharmacokinetic studies well as safety analysis of MaxCmin 1 data, such test of efficacy is requested as a Phase 4 commitment from the applicant.

C. Safety

In the MaxCmin 1 study, adverse events (AEs) from 306 patients who were randomized to one of two treatment arms and received at least one dose of the study drug were included in the 48 week safety analysis. In general, the safety profile of the FTV/RTV regimen as used in the MaxCmin 1 study was comparable to that of unboosted FTV. The most common AEs were gastrointestinal in nature. No new safety issues were identified upon co-administration of low dose RTV with FTV in this study. Lastly, postmarketing safety data as supplied from the applicant and from the Agency's Office of Drug Safety did not reveal additional safety concerns associated with co-administration of SQV and RTV.

Limitations of the MaxCmin 1 safety analysis include the lack of quality checks for AEs and expansion of time windows outside of those specified in the study protocol in order to assign laboratory values to study visits. These limitations may explain some of the minor discrepancies between the Agency's analysis of the safety data and that of the applicant. However, such limitations should not significantly affect the overall findings of the safety analysis.

Based on previous data as well as those from the EPIMED 1 study, the safety profile of the INV/RTV combination regimen is anticipated to be similar to that of the FTV/RTV regimen. Since the Capmul excipient in FTV has been associated with increased gastrointestinal adverse events, it is possible that the INV/RTV regimen is better tolerated that the FTV/RTV combination in some patients.

In principle, the co-administration of RTV with FTV or INV may expose patients to adverse events previously associated with RTV use. Such risks are likely to be relatively low (as compared to higher doses of RTV historically used to treat HIV infection) since the total daily dose of RTV to be used in the proposed combination regimens is [redacted] mg/day. However, drug-drug interactions that have been described in the RTV product label should be included in the product labels for FTV and INV. Moreover, additional drug-drug interaction studies and pharmacokinetic studies in certain patient populations are warranted (see Special Populations, below).

D. Dosing

The applicant selected the FTV 1000 mg with RTV 100 mg twice daily combination dosing regimen to maximize the patient exposure to SQV while minimizing RTV-associated adverse events. The EPIMED 1 study, in which SQV exposure generated by the proposed FTV/RTV and INV/RTV BID regimens were examined in HIV-infected adults, has been reviewed in detail by Dr. Jen DiGiacinto, the Biopharmaceutics Reviewer. In the EPIMED 1 study population, INV/RTV 1000 mg/100 mg BID was deemed not to be bioequivalent to FTV/RTV 1000 mg/100 mg BID. However, SQV exposures generated from both combination regimens were at least equivalent to that of the currently approved and recommended FTV dosing regimen (1200 mg TID). Thus, both regimens are expected to achieve SQV exposure required to inhibit HIV replication.

E. Special Populations

In the applicant's analysis of MaxCmin 1 efficacy data, there were no significant effects of gender and ethnic background on the efficacy parameters as defined in the MaxCmin 1 protocol. Please refer to Dr. Zhou's review for the Agency's statistical analyses.

No significant information is provided regarding the use of the proposed combination regimens in geriatric or pediatric populations. With regard to the pediatric population as well as in patients with impaired hepatic function, no plans to study the proposed combination regimens are evident. The Division has requested such studies as postmarketing commitments.

Both formulations of SQV as well as RTV are Category B with regard to use during pregnancy. No new information on the effects of the proposed combination regimens in pregnant women are presented in these supplemental NDAs.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, applicant's Proposed Indication(s), Dose, Regimens, Age Groups

Trade (Generic) Names: Fortovase® (saquinavir); Invirase® (saquinavir mesylate).

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).

Approved dosage forms: soft-gelatin capsules containing 200 mg saquinavir free base (Fortovase®); hard-gelatin capsules containing 200 mg saquinavir mesylate (Invirase®).

Currently approved dosing regimens: FTV: 1200 mg TID; INV: 600 mg TID.

Saquinavir (SQV) is a competitive inhibitor of the protease encoded by the human immunodeficiency virus (HIV). Because of its mechanism of action, SQV inhibits the post-translational modification of HIV-encoded gag-pol polyproteins and thereby suppresses the formation of infectious HIV virions. 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 called Invirase® (abbreviated as INV throughout this review). In 1997, a soft-gel 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.

The two formulations, INV and FTV, differ with respect to SQV exposure following oral administration. When FTV is taken at the recommended dose of 1200 mg TID, the total exposure to SQV is about 8 to 10 fold higher than the SQV exposure following the recommended INV dose of 600 mg TID. Given such differences, the previously approved package insert for INV stated that: 1) FTV was the recommended formulation when SQV was to be used as part of an antiretroviral regimen, and 2) INV may be considered for use when combined with antiretroviral agents that significantly inhibited the metabolism of SQV. However, no recommendations on the dosing regimen for use with such metabolic inhibitors were given in the previous package insert.

Since the approval of SQV, co-administration of FTV or INV with another protease inhibitor (PI), ritonavir (RTV; Norvir®, Abbott Laboratories) has been used in clinical practice to treat HIV infection. When administered with FTV or INV, RTV inhibits the metabolism of SQV and thus increases patient exposure to SQV. Twice daily administration of SQV (typically 400 mg) with RTV 400 mg has been used in clinical practice as a "dual protease" regimen for HIV infection. In addition, co-administration of INV with RTV has been used in patients who experienced Capmul-associated

gastrointestinal adverse events while taking FTV. However, adverse events that have previously been associated with RTV use were noted among patients receiving RTV at 400 mg twice daily with SQV.

In these two supplemental NDAs, the applicant proposes new dosing recommendations for 1000 mg of INV (NDA 20628) or FTV (NDA 20828) as twice daily (BID) co-administration with 100 mg RTV. 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. Moreover, the relatively low doses of RTV is expected to reduce the risk for RTV-associated adverse events. The applicant states that the proposed BID dosing regimens will generate patient exposures to SQV that are more sustained than those from the previously approved 1200 mg FTV TID regimen. Moreover, the applicant proposes to alter the INV dosing recommendation from the currently approved 600 mg TID regimen to 1000 mg BID with concomitant administration of RTV at 100 mg BID. Lastly, the

The pivotal clinical study that is submitted in support of these indications, MaxCmin 1, examined the safety and efficacy of FTV/RTV 1000 mg/100 mg BID when administered for 48 weeks to a heterogeneous population of treatment-naïve and treatment-experienced HIV-infected subjects. In this Phase IV, randomized, open-label, parallel group, multi-center trial, subjects in the comparator arm of the MaxCmin 1 study received a twice daily regimen of 100 mg RTV and 800 mg of another PI, Indinavir (Crixivan®, Merck; abbreviated as IDV throughout this review). This study was conducted and analyzed by the . The results from the MaxCmin 1 study were published during the course of the review process of these NDAs (Dragsted, U.B., et al. for the MaxCmin 1 Trial Group. Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin 1 trial. J. Infect. Dis. 188: 635-42, 2003).

The applicant also submitted the results from a pharmacokinetic (PK) study, EPIMED I, that examined the SQV exposures in HIV-infected patients following FTV/RTV 1000 mg/100 mg BID and INV/RTV 1000 mg/100 mg BID. The applicant uses the EPIMED 1 study as a pharmacological "bridge" to extend the efficacy and safety profiles of the FTV/RTV regimen (as shown in the MaxCmin 1 study) towards the proposed INV/RTV twice daily regimen.

Of note, current product labels for INV and FTV indicate that SQV pharmacokinetics have not been investigated in pediatric patients (< 16 years of age) or patients > 65 years old. In these NDAs, no formal studies are submitted in support of SQV use in pediatric or geriatric populations.

B. State of Armamentarium for Indication(s)

Currently, there are four classes of drugs that have been approved to treat 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 four antiretroviral agents to drastically reduce viral replication and thus reconstitute the immune system.

To potentially improve tolerability and patient adherence while achieving sufficient PI levels, efforts to develop RTV-boosted PI regimens have been noted. To date, a PI that is co-formulated with low-dose RTV (Lopinavir + RTV; Kaletra®, Abbott Laboratories) has been approved for treatment of HIV infection. Moreover, for a subset of recently approved PIs such as amprenavir, atazanavir, and fosamprenavir, product labels bear dosing recommendations to be followed when administering these drugs in conjunction with low doses of RTV.

C. Important Milestones in Product Development

In 1995, INV was approved under NDA 20628 by the Agency to be used in combination with other antiretroviral agents for the treatment of HIV infection. For the same indication, FTV was approved under NDA 20828 by the Agency in 1997.

D. Other Relevant Information

According to the applicant, FTV and INV have been approved in 61 and 66 countries respectively, including those in the European Union. Neither FTV nor INV has been withdrawn from the market in any country. The EMEA approved the combination dosing of FTV and RTV as 1000 mg/100 mg BID and INV and RTV as 1000 mg/100 mg BID in August and September 2002, respectively.

E. Important Issues with Pharmacologically Related Agents

Several PIs used to treat HIV infections have significant effects on the hepatic cytochrome P450 enzyme system. Based on its inhibitory effects on CYP3A4, RTV has been shown to induce a number of clinically significant drug-drug interactions. Such effects may be of clinical importance even at the low dose (100 mg BID) of RTV to be used with FTV and INV in the proposed BID regimens. The applicant seeks in these NDA supplemental applications to update the product labels for FTV and INV to include a number of such drug-drug interactions involving RTV.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

This Clinical Review includes clinically relevant findings from the Biopharmaceutics and the Statistics Reviews. The efficacy data from the MaxCmin 1 study is reviewed in detail

by Dr. Susan Zhou, the Statistical Reviewer. Clinically relevant portions of Dr. Zhou's review are incorporated into Integrated Review of Efficacy (Section VI) of this Clinical Review. The EPIMED 1 study as well as a number of drug-drug interaction study reports were reviewed in detail by Dr. Jen DiGiacinto, the Biopharmaceutics reviewer. Clinically relevant findings from Dr. DiGiacinto's review are described in the Human Pharmacokinetics and Pharmacodynamics (Section III) of this Clinical Review. Of note, the safety data for EPIMED 1 is reviewed in the Integrated Review of Safety (Section VII) of this Clinical Review. Lastly, findings and recommendations of the Agency's Office of Drug Safety (ODS) regarding adverse events associated with SQV and RTV co-administration are included in the Appendix of this Clinical Review. With regard to other disciplines, no new clinically relevant findings are included in their respective reviews.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The applicant selected the dosing regimen of FTV/RTV 1000/100 mg BID because of its ability to achieve C_{min} values equal to or greater than the average C_{min} achieved by the FTV 1200 mg TID regimen. In previous studies with co-administration of SQV with RTV, higher doses of RTV (up to 400 mg BID) led to increased incidence of RTV-associated adverse events. The applicant states that the co-administration of FTV or INV did not significantly affect the PK of RTV at doses used in previous studies.

Data from the EPIMED 1 study suggest that increases in SQV PK parameters were observed when FTV/RTV 1000 mg/100 mg BID and INV/RTV 1000 mg/100 mg BID were administered to HIV infected subjects. As described in greater detail in the Biopharmaceutics Review of the EPIMED I data, the following points may be made: 1) in the HIV-infected patient population, INV/RTV 1000 mg/100 mg BID was not deemed to be bioequivalent to FTV/RTV 1000 mg/100 mg BID; and 2) given the SQV PK parameters that were derived from the EPIMED 1 study population, SQV exposures generated from both regimens are at least equivalent to that of the currently approved and recommended FTV dosing regimen (1200 mg TID).

The inclusion of RTV in the FTV and INV product labels require that drug-drug interactions that occur with RTV use are incorporated in the product labels. To this end, the applicant has included in these NDAs a number of drug-drug interaction studies with RTV in support of the proposed combination dosing. These study reports are reviewed in detail by Dr. Jen DiGiacinto, the Biopharmaceutics Reviewer. Based on the review of such drug-drug interaction studies, the applicant is asked to perform several additional drug-drug interaction and PK studies as Phase IV commitments.

In these NDAs, no new data on the basic PK properties, including effects of impaired hepatic and renal functions, body size/weight, gender, and/or race on such PK properties, of the FTV and INV formulations of SQV are presented.

B. Pharmacodynamics

No new pharmacodynamic data are included in these supplemental NDA submissions.

IV. Description of Clinical Data and Sources

A. Overall Data

The supplemental application under NDA 20828 is comprised of 20 volumes in paper submission format that collectively contain the results of the MaxCmin 1 and the EPIMED I studies. Also included in these volumes are supplemental materials such as previously conducted studies and relevant literature reports. The accompanying supplemental application for NDA 20628 contains three paper volumes bearing additional materials, including postmarketing data for SQV co-administered with RTV. Lastly, during the review process, 11 additional paper volumes of the applicant's postmarketing surveillance reports for SQV were provided and reviewed in the Appendix of this Clinical Review.

Concomitant with the paper volumes, the datasets for the MaxCmin 1 study, including individual patient CRFs, were submitted as an electronic submission (esub) to the Agency. The datasets for the EPIMED I study were initially submitted in a non-esub compatible format (Microsoft Excel); upon the Agency's request, the EPIMED I datasets were resubmitted in esub-compatible format in June 2003. Lastly, in reference to additional requests from the Division, revised electronic datasets and statistical analyses for the MaxCmin 1 study were submitted in an esub-compatible format in October 2003.

B. Tables Listing the Clinical Trials

A clinical study, MaxCmin 1, was reviewed in detail with respect to safety and efficacy. In addition, the safety profiles of the proposed SQV/RTV combination regimens as used in the EPIMED I study were reviewed. With regard to previously conducted studies that are relevant to these two supplemental NDAs, the following comments may be made:

- NV 15355: A randomized, parallel arm, comparative, open label, multi-center study of the activity and safety of two formulations of saquinavir in combination with two nucleoside antiretroviral drugs in treatment-naïve patients. In 1997, the Agency reviewed the 16 week safety and efficacy data for NV 15355. However, as described in the current NDA application, the applicant intends to include the 48 week safety data from the NV 15355 study in the proposed labels for FTV and INV. Thus, the updated safety data as provided in the NV 15355 Final Report (included in these supplemental NDAs) are summarized in the Appendix section of this Clinical Review.

- NV 15182: A multicenter, open label study of safety and activity of FTV 1200 mg TID in combination with other antiretroviral drugs for at least one year in HIV-infected, PI-naïve or –experienced patients. During the 1997 FTV approval process, the 48 week safety update and the 24 week safety and efficacy data were reviewed. In these NDAs, the applicant provides the 60 week efficacy and safety data as summarized in the Final Report of this study. Such data that are relevant to the proposed SQV/RTV combination regimens are summarized in the Appendix of this Clinical review.

- Summary Reports and reprints of articles describing several PK and safety/efficacy studies with once-daily dosing of SQV/RTV combinations are summarized in the Appendix of this Clinical review. Since the applicant is not

C. Postmarketing Experience

The NDA 20628 supplemental application contains the applicant's own postmarketing data for adverse events associated with SQV co-administered with RTV. In addition, 11 additional volumes of the applicant's postmarketing Periodic Safety Update Reports for SQV from 1995 to November 2002 were provided and reviewed. Lastly, the Agency's Office of Drug Safety was consulted regarding adverse events reported to the FDA MedWatch database with SQV/RTV co-administration. These postmarketing data are reviewed in the Appendix of this Clinical Review.

D. Literature Review

During the course of this review, the following articles and abstracts with direct relevance to the review process were used:

- Arnaiz, J.A., et al. for the BEST Study Team. Continued indinavir versus switching to indinavir/ritonavir in HIV-infected patients with suppressed viral load. AIDS 17: 831-840, 2002. The applicant compares the safety profile of the IDV/RTV arm in the MaxCmin 1 study with that of the BEST study.
- Dragsted, U.B., et al. for the MaxCmin 1 Trial Group. Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus type 1-infected patients: the MaxCmin 1 trial. J. Infect. Dis. 188: 635-42, 2003. This article that describes the MaxCmin 1 study was published during the course of this review.
- Youle, M. et al., for the MaxCmin 2 Trial Group. The final week 48 analysis of a Phase IV, randomized, open-label, multi-center trial to evaluate safety and efficacy of lopinavir/ritonavir (400 / 100 mg BID) versus saquinavir/ritonavir (1000 / 100 mg BID) in adult HIV-1 infection: the MaxCmin 2 trial. Abstract LB23, the 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, 2003.

V. Clinical Review Methods

A. How the Review was Conducted

The MaxCmin 1 study was reviewed for safety and efficacy. The applicant's analysis and conclusions regarding this study were independently confirmed by the Agency. Dr. Susan Zhou performed the statistical analyses of the data, particularly the efficacy analysis. The Medical Officer used [redacted] to review other aspects of the MaxCmin 1 study analysis, including patient demographics, patient exposure, 48-week patient disposition, adverse events and laboratory safety data. Where relevant in this Clinical Review, references below each of the figures and tables refer to the relevant page(s) of the applicant's NDAs. Tables generated from the Agency's analysis refer to the applicant's dataset(s) used in such analysis.

B. Overview of Materials Consulted in Review

The 20 paper volumes of supplemental NDA 20828 application and the three paper volumes submitted under NDA 20628 were reviewed. The initial date of submission for the two supplemental NDAs was February 20, 2003. Also reviewed were: 1) the applicant's esub datasets for MaxCmin 1; 2) the Final Study Reports for the MaxCmin 1 and EPIMED 1 studies; 3) literature cited as listed above; 4) postmarketing data from the applicant as well as those from the Agency's MedWatch database (as described in the Consultation Report from the Agency's Office of Drug Safety); 5) copies of the European Package Inserts for FTV and INV that were approved by EMEA; 6) additional 11 paper volumes of the applicant's postmarketing data for SQV (submitted August 8, 2003); and 7) MaxCmin 1 datasets that were electronically submitted on February 20, 2003 and October 15, 2003 as well as EPIMED I datasets that were submitted on February 20, 2003 and July 9, 2003.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

During the review of these supplemental NDAs, site inspections by the Division of Scientific Investigations were not requested by the Division of Antiviral Drug Products.

With regard to the EPIMED 1 study, the applicant states that no critical GCP deviations were observed that in the auditor's opinion would negatively impact on the data generated and the use of this study to support the filing of the supplemental NDA.

With respect to the MaxCmin 1 study, the applicant states that no inconsistencies were found in the safety data. Any omissions from the MaxCmin 1 database of virological failures were detected, immediately corrected, and reanalyzed. The reanalysis confirmed that p-values comparing treatment arms for differences or for equivalence did not perceptibly change that would alter the conclusions reached by the [redacted] investigators.

During the course of the NDA review process, three issues regarding the quality assurance of the MaxCmin 1 datasets and analysis became evident. First, summaries and WHO ICD 10 coding of all adverse events (grades 1-4) were not subjected to thorough quality check (pp. 14-35, 14-39 of NDA 20828). Second, as mentioned in the MaxCmin 1 Final Report, the applicant extended the study visit windows to utilize the laboratory values that were collected 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 (p. 14-25, NDA 20828). Such extension of the time windows were larger than those specified in the MaxCmin 1 protocol, and may explain some of the discrepancies between the applicant's analysis of the data and that performed by the Division. Third, in response to the Division's requests, the applicant provided during the review process revised analyses of the MaxCmin 1 efficacy data and additional datasets on patient demographics. Analysis of such revised datasets did show some differences in the efficacy data as provided in the MaxCmin 1 study report and as analyzed by the Division. In this Clinical Review, these points will be addressed in relevant Sections below. Despite these issues, in the opinion of this Medical Officer, the safety and efficacy of the proposed FTV/RTV combination regimen as studied in the MaxCmin 1 study supports the approval of the proposed combination regimens.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The applicant notes that the MaxCmin 1 study was conducted in accordance with ICH-GCP guidelines and all applicable regulations, including the Declaration of Helsinki. Furthermore, the applicant notes that the protocol was reviewed and approved by the appropriate [redacted] A copy of the protocol, the Patient Information Sheets, and the Patient Consent Forms are included in the NDAs. According to the applicant, monitors from [redacted] periodically contacted each of the MaxCmin 1 study sites or performed on-site visits to evaluate the documentation of patient's informed consent and other issues according to the standard operating procedures of [redacted] Lastly, the applicant states that there was appropriate documentation to confirm that the MaxCmin 1 study was conducted according to accepted ethical principles and was monitored as described in the protocol.

The applicant notes that the EPIMED I study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by an ethics committee [redacted] Furthermore, the investigators for the EPIMED I study adhered to the provisions set out in GCP Guidelines. A copy of the study protocol as well as copies of the Patient Information and Consent Forms are included in the NDAs.

Thus, given the information summarized above, the MaxCmin 1 and EPIMED 1 studies appear to have been conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

In the NDA 20828 application, the applicant provided Form FDA 3454 with regard to the required certification and disclosure of financial interests of the MaxCmin 1 study investigators. On this form, 27 of the 28 Principal Investigators and 121 out of 140 Sub-Investigators had nothing to report. According to the applicant, due diligence was made to obtain the requisite information from the single Principal Investigator and 29 Sub-Investigators who did not sign the requisite financial disclosure form. The reasons why such information was not obtained are attached to the Form 3454.

In this application, the applicant reports that the principal clinical investigator for the EPIMED I study had nothing to report with regard to the required certification and disclosure of financial interests as submitted on FDA Form 3454.

Thus, financial disclosures as provided by the applicant are consistent with the notion that the findings of the MaxCmin 1 and EPIMED 1 studies are independent of the financial interests of the various study investigators.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Results from the MaxCmin 1 study show that the antiretroviral effects of FTV/RTV 1000/100 mg BID are comparable to those seen with IDV/RTV 800/100 mg BID. In the MaxCmin 1 study, a heterogeneous population of antiretroviral-naïve and –experienced HIV infected patients who received the FTV/RTV BID regimen achieved similar levels of HIV RNA suppression and increases in the CD4+ cell counts as those who received the comparator IDV/RTV regimen. Of note, the analysis of efficacy endpoints as defined in the MaxCmin 1 protocol and as shown in the Final Study Report did not conform to the DAVDP's TLOVR algorithm. In response to the Division's requests, the applicant provided a series of revised efficacy data analyses based on all study visits or scheduled visits only, inclusion or exclusion of data from five patients whose samples were analyzed for HIV RNA levels using the [redacted], and 50 or 400 copies/mL as LLQ. In general, the number of subjects in the FTV/RTV arm who achieved the LLQ over the course of the 48 week study was slightly greater than those in the comparator arm; however, in most cases, such difference was not statistically significant. Similarly, a revised dataset bearing the CD4+ cell counts was provided. In general, such datasets confirmed the applicant's statement that in the MaxCmin 1 study, increases in CD4+ cell counts were seen in both arms of the study and that the differences in the CD4+ cell count increases were not statistically significant between the two arms. Please refer to Dr. Zhou's Statistical Review regarding the Agency's full analysis of efficacy parameters, including CD4+ cell count and special populations. The fact that the IDV/RTV comparator regimen used in the MaxCmin 1 study has not been approved by the Agency for treatment of HIV infection remains a limitation of the efficacy analysis.

B. General Approach to Review of the Efficacy of the Drug

The applicant's definition of virological failure as described in the MaxCmin 1 protocol and analysis of the efficacy data as shown in the MaxCmin 1 Study report were reviewed. However, there were significant differences between the between the applicant's analysis of efficacy data and those specified in the recent Guidance Document (Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval, October 2002). Thus, the applicant resubmitted the efficacy analysis for the MaxCmin 1 data following the time to loss of virologic response (TLOVR) algorithm as defined by DAVDP for the two arms of the study through week 48. The applicant's revised analysis of the incidence of virological failure and changes in CD4+ cell count for the two arms during the course of the MaxCmin 1 study were confirmed by Dr. Susan Zhou, the Statistical Reviewer. Lastly, the patient demographics were confirmed by this Medical Officer.

C. Detailed Review of Trials by Indication

1. Summary of Study Design-MaxCmin 1 Study.

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 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. Aside from the randomized PI therapy, no other PIs were to be used in these patients except in cases of treatment toxicity or failure. During the course of the study, the investigators were responsible for monitoring of possible drug-drug interactions between any of the PIs and other agents that may be metabolized by the CYP3A4 system.

With respect to study logistics [redacted] developed the protocol and administered the MaxCmin 1 study while the applicant provided financial support for the study. The contract between the two parties included stipulations that the applicant cannot veto the public presentation of the results from the study. A Steering Committee, intentionally devoid of representatives from [redacted] supervised the analysis and presentation of the MaxCmin 1 study data by [redacted] as well as selected members for the Data Safety Monitoring Board.

The dose for IDV/RTV combination regimen was chosen to increase plasma concentrations of IDV while minimizing the toxicities associated with IDV and RTV. As compared to the IDV pharmacokinetic parameters associated with unboosted 800 mg TID regimen, the C_{min} of IDV was higher when administered as 800 mg BID with RTV 100 mg BID. For the MaxCmin 1 study, patients who received IDV/RTV were not under food restrictions but were recommended to maintain fluid intake of > 1.5 liters. Of note, this dosing combination of IDV and RTV has been studied in another clinical trial (the BEST study) that has recently been published (Arnaiz, et al., 2002). The dosing rationale for the FTV/RTV combination regimen has been discussed elsewhere in this review.

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 were: to determine the differences in the CD4 lymphocyte count response; to determine the frequency of subjects with suppression of HIV RNA in the two treatment arms; to assess the safety and tolerability of the two treatment arms; to assess changes in genotypic and phenotypic resistance in plasma HIV-1 over the study period in the two treatment arms; and to determine the concentration of study PIs in plasma approximating the trough levels at weeks 4 and 48 after starting study medication. According to the applicant, data analysis for the last two secondary objectives are ongoing and thus not included in the MaxCmin 1 Final Report.

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.

With regard to changes in antiretroviral therapy, only patients experiencing treatment limiting adverse events or virological failure (as defined in the protocol; see below) were permitted to discontinue the assigned PI regimen. If either of the PIs to which the patients were randomized was likely to be responsible for the treatment-limiting adverse event or virological failure, the dosing of the PIs were to be adjusted with guidance from — With regard to non-PI agents, one or more of such drugs may be discontinued and replaced during the first 24 weeks of the study only in cases of treatment-limiting adverse events, virological, immunological, or clinical failure (see below). However, even when one or more of these criteria were fulfilled, change of the non-PI treatment was not mandatory. During the second 24 week portion of the study, the non-PI treatment could be changed at the discretion of the investigator.

Of note, the applicant reports several instances in which patients receiving FTV/RTV developed gastrointestinal side effects that were at least possibly related to the — component of the FTV formulation. For such patients, 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. Such switching was not considered as a switch in assigned treatment with respect to the applicant's statistical analysis.

2. Study Population-MaxCmin 1 Study.

Major inclusion criteria were:

- Male or female, > 18 years of age.
- HIV-1 infected as documented by a licensed HIV-1 ELISA.

- Women of childbearing potential with a negative serum pregnancy test (beta-hCG) within 28 days of trial day 1.
- Ability to provide appropriate consent.
- All clinical laboratory values must have been considered clinically significant—for the potential response to the planned new regimen—in the opinion of the investigator.
- Fulfillment of at least one of the following five criteria, provided that either (see following inclusion criterion) of the boosted PI-regiments 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 regiment (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 (i.e. loose stool or peripheral dysaesthesia) 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).
- For all five sub-criteria listed above, the *a priori* probability of responding to SQV and IDV, as judged by the investigator, should have been equal. The judgment should have taken into account the factors mentioned below which would preclude enrollment:
    - Prior dose-limiting toxicity to either IDV or SQV (irrespective of dosing).
    - Prior switch away from a regimen that included one but not the other PI (IDV, SQV) because of virological failure, except if resistance testing at time of failure did not show evidence of selective resistance development (not applicable for patients who are PI-naïve). Thus, 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.

- 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. Of those subjects in the FTV/RTV arm, nine withdrew consent/declined participation and one died (see Integrated Review of Safety, below). According to the applicant, the reason for the one patient in the IDV/RTV arm who did not commence the study treatment was unknown.

In the opinion of this Medical Officer, the imbalance of the number of patients who did not start the assigned treatment after randomization (10 in the FTV/RTV arm versus one in the IDV/RTV arm) merits several comments. Since the MaxCmin 1 study was an open-label study, it is possible that such difference may indicate the presence of an underlying systematic bias inherent to the study. It is possible that either the investigators (at each of the study sites and/or those at [redacted] or the patients showed a preference for IDV/RTV regimen. It is also conceivable that the clinical status of patients randomized to the FTV/RTV arm were worse than those of patients in the comparator arm, and thus more patients in the FTV/RTV arm did not start assigned therapy.

The efficacy and safety analyses were performed on the intent-to-treat (ITT) population, which was defined as all study subjects who were randomized to either of the two treatment arms and who were exposed to at least one dose of randomized treatment.

3. Demographic Data and Baseline Characteristics-MaxCmin 1 Study.

The first patient enrolled in the study on September 1, 2000 and enrollment was closed in March 2001. At that time, 317 patients were randomized, 159 to IDV/RTV and 158 to FTV/RTV from 28 sites in 13 countries. A total of 306 subjects received at least one dose of the study drug (ITT population); 158 in IDV/RTV, 148 I the FTV/RTV arm). The following table depicts the demographic data provided by the applicant:

Table 1. Baseline Parameters According to Treatment Arm.

Baseline Parameter	IDV/RTV	FTV/RTV	Total

	N = 158	N = 148	N = 306
Race (N, %)			
White	129 (82)	127 (86)	256(84)
Black	19 (12)	14 (9)	33 (11)
Asian	6 (4)	1 (1)	7 (2)
Other	4 (3)	6 (4)	10 (3)
Gender			
Male	117 (74)	122 (82)	239 (78)
Female	41 (26)	26 (18)	67 (22)
HIV Exposure Group			
Homosexual/Bisexual	74 (47)	76 (51)	150 (49)
IV Drug Use	16 (10)	19 (13)	35 (11)
Hemophiliac	6 (4)	2 (1)	8 (3)
Transfusion	0 (0)	4 (3)	4 (1)
Heterosexual	55 (35)	47 (32)	102 (33)
Unknown	7 (4)	0 (0)	7 (2)
Age (Median, IQR)	40 (34-46)	39 (34-48)	39 (34-47)
Origin			
Same as center	114 (72)	99 (67)	213 (70)
Europe	11 (7)	21 (14)	32 (10)
Africa	15 (9)	14 (9)	29 (9)
America	10 (6)	11 (7)	21 (7)
Asia	6 (4)	1 (1)	7 (2)
Other	0 (0)	2 (1)	2 (1)
Unknown	2 (1)	0 (0)	2 (1)
Region**			
Argentina	28 (18)	27 (18)	55 (18)
Scandinavia	67 (42)	61 (41)	128 (42)
C. Europe	20 (13)	17 (11)	37 (12)
S. Europe	14 (9)	15 (10)	29 (9)
NW Europe + USA	29 (18)	28 (19)	57 (19)
Body Mass Index* (Median, IQR)	24 (22-26)	23 (21-25)	24 (21-26)
Antiretroviral naïve	34 (22)	42 (28)	76 (25)
PI-Naïve	59 (38)	61 (41)	120 (39)
PI-experienced VL ≥ 400 copies/mL***	39 (25)	35 (24)	74 (25)
PI-experienced* VL < 400 copies/mL	59 (38)	52 (35)	111 (36)
CDC Category C	45 (28)	48 (32)	93 (30)
HIV-RNA* (copies/ml $\log_{10}$) (median, IQR)	3.9 (1.7-5.2)	4.0 (1.7-5.1)	3.9 (1.7-5.1)
HIV-RNA* < 400 copies/mL	62 (39)	56 (38)	118 (39)
CD4 cell count* (10^6/L)	280 (139-453)	272 (135-420)	277 (137-450)
CD4 cell count at nadir (10^6/L)	119 (47-225)	107 (33-195)	110 (40-205)

*: these variables include missing information and thus the denominator is less than the number of subjects who received treatment.

**: Scandinavia includes Denmark and Norway, C. Europe includes Germany, Switzerland, and Austria, S. Europe includes Italy, Portugal, and Spain and NW Europe includes Belgium, the UK and Holland.

***: In the MaxCmin 1 Final Study report, the VL is listed as "= 400 copies/mL." It is assumed by this Medical Officer that patients listed in this row bore HIV RNA loads ≥ 400 copies/mL.

Source: NDA 20828 p. 14-42.

The applicant's comment regarding the missing information is taken to mean that for a subset of variables, not all patients had values/numbers and thus calculations to derive the median and IQRs for these variables used only values that were available.

The applicant notes that the majority (84%) of the patients enrolled in this study were Caucasian and male (78%) who were infected through sex with other men (49%). The

median age was 39 years. The demographics and baseline HIV disease characteristics appear balanced between the treatment arms with respect to age, gender, CD4+ count, viral load, HIV risk factors, body mass index, and treatment-naïve and treatment–experienced (PI naïve or experienced, HIV viral load < or > 400 copies/mL). Such demographics reflect the heterogeneous population of HIV-infected patients that were enrolled through the relatively complex entry criteria. Lastly, it is noted by this Medical Officer that there was a slightly greater proportion of patients in the FTV/RTV arm that were treatment-naïve at baseline as compared to those in the IDV/RTV arm (28% versus 22%, respectively).

For the MaxCmin 1 patient population, the summary statistics showing the prior antiretroviral treatment history and the treatment regimen at screening and at baseline are shown below (Tables 2 - 4). The applicant has listed each individual drug according to its drug class. In the previous treatment regimens, the most frequently used NRTI drugs were lamivudine and zidovudine, while indinavir was the most frequently used PI. In both treatment arms of the MaxCmin 1 study, the patterns and types of antiretroviral drugs to which the patients were exposed before or during the study appear balanced. The data shown in these tables are indicative of the regimens most commonly used to treat HIV infection during the time in which the MaxCmin 1 study was conducted. The applicant notes that relatively few patients were treated with NNRTIs prior to enrollment into the study and at screening as well as at baseline.

Table 2. Antiretroviral Exposure Prior to Baseline According to Treatment Arm (ITT).

	IDV/RTV		**FTV/RTV**	
Drug combination	# (%) exposed	Median exposure time (IQR) (weeks)	# (%) exposed	Median exposure time (IQR) (weeks)
NRTIs				
Abacavir	14 (9)	25 (3-44)	10(7)	23 (6-38)
Didanosine	41 (26)	40 (22-94)	44 (30)	48 (18-95)
Lamivudine*	112 (71)	174 (95-228)	94 (64)	168 (105-213)
Stavudine	53 (34)	86 (33-145)	46 (31)	134 (66-184)
Zalcitabine	11 (7)	33 (21-96)	10 (7)	89 (12-162)
Zidovudine*	106 (67)	200 (94-267)	97 (66)	155 (67-246)
Combivir	65 (41)	101 (61-128)	48 (32)	79 (54-111)
PIs				
Indinavir	48 (30)	159 (108-200)	40 (27)	163 (93-190)
Nelfinavir	35 (22)	83 (30-125)	27 (18)	73 (37-105)
Ritonavir	30 (19)	64 (18-163)	35 (24)	112 (13-175)
Fortovase	20 (13)	86 (25-1380	18 (12)	82 (9-118)
Invirase	8 (5)	74 (27-92)	13 (9)	75 (54-86)
NNRTIs				
Efavirenz	13 (8)	56 (26-81)	9 (6)	36 (17-64)
Nevirapine	20 (13)	42 (5-96)	17 (11)	73 (20-102)

Source: NDA 20828 p. 14-43.

Table 3. Ongoing Antiretroviral Therapy at Time of Screening (ITT, non-treatment naïve subjects only).

Drug Combination	**IDV/RTV** (#, %)	**FTV/RTV** (#, %)
NRTIs		
Zidovudine + lamivudine	55 (44)	46 (43)

Zidovudine + didanosine	2 (2)	4 (4)
Stavudine + didanosine	8 (6)	4 (4)
Stavudine + lamivudine	21 (17)	24 (23)
Zidovudine + lamivudine + abacavir	5 (4)	3 (3)
Other combinations	5 (4)	4 (4)
Only 1 NRTI	2 (2)	1 (1)
No NRTIs	26 (21)	20 (19)
PIs		
Indinavir	39 (31)	28 (26)
Nelfinavir	25 (20)	19 (18)
Ritonavir	7 (6)	6 (6)
Invirase	2 (2)	0 (0)
Fortovase	2 (2)	2 (2)
2 PIs	5 (4)	13 (12)
No PIs	44 (35)	38 (36)
NNRTIs		
Efavirenz	5 (4)	5 (5)
Nevirapine	8 (6)	10 (9)
No NNRTI	111 (90)	91 (86)
Total number of subjects	124	106

Source: NDA 20828 p. 14-44.

Table 4. Antiretroviral Therapy at Baseline According to Treatment Arm (ITT).

Drug Combination	**IDV/RTV (#, %)**	**FTV/RTV (#, %)**
Zidovudine + lamivudine	87 (55)	83 (56)
Zidovudine + didanosine	4 (3)	5 (3)
Stavudine + didanosine	12 (8)	11 (7)
Stavudine + lamivudine	31 920)	31 (21)
Zidovudine + lamivudine + Abacavir	1 (1)	1 (1)
Other combinations	17 (11)	11 (7)
Only 1 NRTI	5 (3)	4 (3)
No NRTIs	1 (1)	2 (1)
NNRTI	6 (4)	7 (5)
PIs	158 (100)	148 (100)
Total number of subjects	158	148

Source: NDA 20828 p. 14-45.

During the course of this review, revised datasets that were designed to aid this reviewer in verifying the demographic data from MaxCmin 1 were provided to the Division. Using the full complement of available datasets, the majority of patient demographic data were confirmed by this Medical Officer with minor discrepancies that do not significantly affect the numbers presented in Table 1. However, even using the updated datasets, this reviewer could not independently confirm the nadir values for the CD4+ cell counts. Moreover, based on the datasets that were provided by the applicant, the demographics with respect to various previous, ongoing, and baseline antiretroviral drug regimens were not able to be confirmed by this Medical Officer. These limitations did not significantly affect the overall conclusions of this Clinical Review.

4. applicant's Analysis Plan in the Final Report of the MaxCmin 1 study and as revised by the Agency's request.

Overview of applicant's Efficacy Analysis Plan.

For efficacy analysis by the applicant as well as that by the Agency, all 306 subjects in the MaxCmin 1 study who took at least one dose of study drug (ITT population) were included. The study was designed and powered to show or reject equivalence for the incidence of virological failure (as defined in the MaxCmin 1 protocol) between the two study PI regimens. The sample size of 150 per group was based on the assumption that if underlying failure rates were 20% in both groups, there is an 80% chance that the 95% confidence interval for the difference in failure rates will exclude a difference greater than 15% in either direction.

The primary efficacy parameter as defined in the MaxCmin 1 protocol was the incidence of virological failure, i.e. for subjects entering the study with a viral load of < 200 copies/mL, a confirmed HIV-RNA value of ≥ 200 copies/mL, and for subjects entering the study with a viral load ≥ 200 copies/mL, either any rise in HIV-RNA of ≥ 0.5 logs and/or a viral load of $\geq 50{,}000$ at > 5 weeks after baseline, $\geq 5{,}000$ at > 14 weeks after baseline; or ≥ 200 at > 27 weeks after baseline. All cases of suspected virological failure were to be confirmed by a second HIV-RNA determination performed at least two weeks later or as soon as possible thereafter, even if the first HIV-RNA value identifying failure was measured at the week 48 visit. Once the virological failure was confirmed, then the time of virological failure was defined as the time of the first measurement greater than the limits shown above.

As described by the applicant, secondary efficacy parameters included: proportion of subjects with HIV RNA < 50 and < 400 copies/mL at 24 and 48 weeks; proportion of subjects with virological failure at 24 and 48 weeks; changes in CD4+ cell count from baseline after 24 and 48 weeks; time to/reasons for discontinuation of randomized treatment; immunological failure (as compared to baseline CD4+ cell count, a decrease in the CD4+ cell count of more than 50% on two consecutive occasions at least one week apart, if the baseline CD4+ cell count was more than 150×10^6 /L; for patients with baseline CD4+ cell counts between 100-150 $\times 10^6$ / L, a decrease in the CD4+ cell count to $< 50 \times 10^6$ / L; and for those with baseline CD4 cell counts $< 100 \times 10^6$ / L, a decrease in the CD4+ cell count of $< 25 \times 10^6$ / L); and clinical failure (development of a new AIDS defining event or relapse of a previously successfully treated AIDS-defining event).

The original study protocol stipulated that the proportion of patients with virological suppression (either < 100 or < 400 copies/ml) would be assessed as a function of time during the study. The 100 copies/ml cutoff was initially chosen since at the start of the study, a number of study sites used an assay with a lower limit of detection of 80 copies/ml. However, after the study was started, all stored plasma from sites using a higher cutoff than 50 copies/ml were retested. Thus, all analyses in which the protocol stipulated a cutoff of 100 copies/ml were changed to a cutoff of 50 copies/ml.

During the course of this review, a number of issues regarding HIV RNA measurements were identified. First, the electronic dataset bearing the baseline HIV RNA values was found to contain data from 69 subjects that used assays such as the [redacted] assay that were different from the protocol-specified Roche Ultrasensitive HIV RNA assay. Second, HIV RNA values obtained from unscheduled clinic visits that were distinct from protocol-scheduled visits were included in the datasets. Third, it was unclear from the applicant's Final Report whether or not HIV RNA measurements from assays with varying lower limits of detection were included in the efficacy analysis. Lastly, the efficacy analysis that was presented by the applicant was different from the Division's TLOVR algorithm/analysis.

To address these issues and in response to the Division's requests, the applicant resubmitted the efficacy data as analyzed by the Division's TLOVR algorithm. Of note, all HIV RNA levels from scheduled visits were tested using the Roche Ultrasensitive assay and thus are measured to the same level of accuracy. In contrast, the applicant notes that the unscheduled viral loads were never retested at a central location and thus have different LLQ values. In the applicant's MaxCmin 1 study report, such results were included in the primary analysis for confirmatory purposes only. Lastly, HIV RNA levels from five patients were measured with the [redacted] with LLQ of 80 copies/mL; these values are identified in the revised datasets. Thus, the applicant resubmitted the efficacy analysis using scheduled or unscheduled visits, LLQ = 50 or 400 copies/mL, and with or without inclusion of [redacted] results. These results are discussed below. It should be noted that the results from the TLOVR analyses are slightly different than those in the MaxCmin 1 Final Report and the published article describing this study (Dragsted, et al., 2003).

Another limitation of efficacy and safety analyses is the definition of time windows for patient visits. The MaxCmin 1 Final Study report states that for purposes of analysis and to assign a study visit to all follow-up visits, the time windows for all scheduled study patient visits were extended as follows: week 4 visit included data from day 1 to beginning of week 10, week 12 visit included weeks 10-21, week 24: weeks 21-33, week 36: weeks 33-week 45, week 48: weeks 45-60; and all data collected after week 60 were censored (NDA 20828, p. 14-36). It is assumed by this reviewer that for the primary efficacy analysis as resubmitted by the applicant, HIV RNA measurements from scheduled visits followed the protocol-defined windows and those from unscheduled visits are identified as such. However, for other efficacy analysis (e.g. CD4+ counts) and safety data analysis, such extension of study windows as described by the applicant may explain some differences between the data analysis by the applicant and the Division (see below).

Primary efficacy parameter:

As presented in the MaxCmin 1 Final Report, the applicant's analysis of virological failure is as follows:

- "Switch included": Switch of randomized treatment was ignored. Events such as death, withdrawal of consent, or loss to follow-up were also considered as virological failure if they occurred before observed virological failure. This was the applicant's primary method of efficacy analysis. According to this method, at the 48 week conclusion of the study, 77 subjects (55 due to observed virological failure and 22 due to loss of follow-up) experienced virological failure. Of these, 41 subjects were in the IDV/RTV arm (of which 76% were due to observed virological failure) and 36 subjects were in the FTV/RTV arm (of which 67% were due to observed virological failure). The applicant states that between the two study arms, there were no statistically significant differences in the median HIV RNA levels at time of failure as well as the number of subjects with HIV RNA levels < 400 copies/mL, and those still on randomized PI at time of failure. For the formal test of proportions of subjects failing at 48 weeks (i.e. as defined in the protocol, whether or not to be able to claim that the difference in success rated between the two treatments is less than 15%), the applicant obtained a p-value of 0.0048, and thus claim statistical significance between the two treatment arms.

- Two supplemental efficacy analyses were also performed: "switch = failure" (switch from randomized treatment, death, withdrawal of consent, and loss of follow-up were all considered as virological failure if observed virological failure had not occurred prior to such events) and "on treatment" (subjects who switched from the randomized treatment were not included for analysis from time of such switch regardless of the reason for such switch). In the "switch = failure" analysis, 128 subjects met the failure criteria (73 due to stopping the randomized treatment and 35 due to observed virological failure; 61 in IDV/RTV arm and 82 in FTV/RTV arm). The risk of virological failure among subjects in the IDV/RTV arm was greater as compared to that among those in the FTV/RTV arm ($p = 0.01$ by the log-rank test; $p = 0.18$ by the proportional hazards test). In the "on treatment" analysis, a total of 35 subjects (20 in IDV arm and 15 in SQV arm) met the failure criteria; this difference was not significant ($p = 0.56$ by log rank test).

In the revised electronic submission from October 2003, the applicant provides the following graphs and tables in response to the Division's requests:

- Response rates according to treatment arm and LOQ level (400 or 50 copies/mL), failure determined on all visits (scheduled and unscheduled) or scheduled visits only, with or without 5 NASBA cases (patients whose HIV RNA levels were measured using an assay with LOQ = 80 copies/mL).
- Kaplan-Meier estimate of the probability of response during 48 weeks of treatment according to TLOVR analysis based on all visits (scheduled and unscheduled) or scheduled visits only, LOQ = 50 or 400 copies/mL, with or without 5 NASBA cases.

- Disposition tables utilizing HIV RNA values from all scheduled and unscheduled visits or scheduled visit only, allowing or disallowing 5 cases with [redacted] and LOQ = 50 or 400 copies/mL.

The disposition tables and the Kaplan-Meier estimates are summarized below:

Table 5. Summary of Disposition Tables Resubmitted by the applicant.

Outcome (1) (Failure determination)	**FTV/RTV (N = 158)** n (%)	**IDV/RTV (N = 159)** n (%)	**p value**
Scheduled and unscheduled visits, LOQ = 400 copies/mL			
Responder	97 (61.4%)	82 (51.6%)	0.078
Scheduled and unscheduled visits, LOQ = 50 copies/mL, with 5 NASBA cases			
Responder	87 (55.1%)	70 (44.0%)	**0.049**
Scheduled and unscheduled visits, LOQ = 50 copies/mL, without 5 NASBA cases			
Responder	83 (54.2%)	70 (44.0%)	0.071
Scheduled visits only, LOQ = 400 copies/mL			
Responder	100 (63.3%)	82 (51.6%)	**0.035**
Scheduled visits only, LOQ = 50 copies/mL with 5 NASBA cases			
Responder	85 (53.8%)	69 (43.4%)	0.064
Scheduled visits only, LOQ = 50 copies/mL without 5 NASBA cases			
Responder	81 (52.9%)	69 (43.4%)	0.092
Reason for Discontinuation (2)			
New CDC-C events	0 (0%)	1 (0.6%)	
Death	1 (0.6%)	1 (0.6%)	
Adverse Event (3)	20 (12.7%)	48 (30.2%)	
Other Reasons:	24 (15.2%)	10 (6.3%)	
Consent withdrawal	5 (3.2%)	3 (1.9%)	
Lost to follow-up	4 (2.5%)	5 (3.1%)	
Never treated	10 (6.3%)	1 (0.6%)	
Other (4)	5 (3.2%)	1 (0.6%)	

1: For each of the six study outcomes, the p values of the comparisons between the responders in each of the study arms is included in the last column. Values < 0.05 are in bold.

2: For each of the six study outcomes, the number of patients in each of the categories under discontinuation are identical except for a minor difference of one patient in the AE column under IDV/RTV arm (47 versus 48 patients). This difference is likely due to the time that this patient reached one of the treatment failure/discontinuation endpoints (loss of virologic response or AE). In the opinion of this Clinical Reviewer, this minor difference does not make a significant change in the interpretation of the data.

3: Per applicant, AEs includes clinical and laboratory AEs.

4: Per applicant, this included non-compliance and protocol violations.

Source: Adapted from NDA 20628/20828 electronic submission Oct. 15, 2003.

Table 6. Summary of Resubmitted TLOVR Analyses and Kaplan-Meyer Estimates.

Basis for TLOVR Analysis/Kaplan-Meyer Estimate of Probability of Response	**p value (Log-Rank Test)**
Scheduled and unscheduled, LOQ = 400 copies/mL	0.0283
Scheduled and unscheduled, LOQ = 50 copies/mL, with 5 NASBA cases	0.0167
Scheduled and unscheduled, LOQ = 50 copies/mL, without 5 NASBA cases	0.0313
Scheduled visits only, LOQ = 400 copies/mL	0.0276
Scheduled visits only, LOQ = 50 copies/mL with 5 NASAB cases	0.0442

Scheduled visits only, LOQ = 50 copies/mL without 5 NASBA cases	**0.0667**

Source: Adapted from NDA 20828 electronic submission Oct. 15, 2003.

As shown above, the p values obtained for the difference between the treatment arms in the number of patients who met the criteria for virological failure were similar (0.035 – 0.092) among the six outcomes of the study population. In two of the six such outcomes, $p < 0.05$ was obtained. With respect to the difference in the probability of virological response (equal to 1 – probability of virological failure) between the two arms of the study, similar range of p values (0.0276 – 0.0667) were obtained among the six outcomes; $p < 0.05$ was obtained for all but one analyses. Thus, in general, the revised TLOVR efficacy analysis for the MaxCmin 1 study population confirm the applicant's assertion that there is a difference between the two treatment arms. However, such differences as shown in six possible outcomes may or may not be statistically significant and appear less robust than the applicant's analysis. Lastly, the disposition of subjects at week 48 were reconfirmed by this Clinical Reviewer using the revised datasets provided by the applicant.

Secondary efficacy parameters:

Proportion of subjects with HIV-RNA < 400 copies/mL or <50 copies/mL: In graphs provided by the applicant, it appears that the proportion of patients with HIV RNA < 400 copies/mL is greater in the FTV/RTV arm as compared to IDV/RTV arm when using the "switch = failure' approach. Similar trends are noted in the "switch included" and "on treatment" approach. However, no statistical analyses are presented to determine whether or not such differences are significant. Given the revised datasets, the applicant's analysis on this parameter was not confirmed during this review process.

Changes in CD4 cell count: With respect to the median CD4 cell count increase from baseline values, the applicant noted that such increases were modest (median changes at week 4: 30.5-35.5; at week 48, 72.5 – 84.5) and no statistically significant differences between the two treatment arms were noted. Similarly, the applicant notes that the median (IQR) time from baseline to increase of > 100 CD4 cells/mL was 15 (5-36) weeks for subjects in the IDV/RTV arm and 12 (4-28) weeks for FTV/RTV arm ($p = 0.48$, log rank test). Lastly, according to the applicant, a total of six subjects met the criteria for immunological failure (four in the IDV/RTV arm, two in the FTV/RTV arm) which precluded formal statistical analysis regarding the differences in these numbers between treatment arms. These numbers were verified by Dr. Susan Zhou; please refer to her Statistical Review for additional details.

Clinical endpoints: The applicant noted that during the course of the study, among subjects on randomized treatment, 20 HIV-associated events and clinical progression (13 CDC category B events and seven category C events) were noted. Of these occurrences, the applicant states that 14 (including four category C events) were among subjects randomized to the IDV/RTV arm, and nine (including three category C events) were noted in subjects in the FTV/RTV arm. Given these low numbers, the applicant did not

perform statistical analysis of these events. In this Medical Officer's review of the datasets, out of 20 total cases of HIV-associated events (category B) and clinical progression to category C, 13 (including four category C events) cases were in the IDV/RTV arm and seven (including three category C events) cases were in the FTV/RTV arm. No statistical analysis of these events were performed during this Clinical Review.

Additional analyses: Given that a heterogeneous population of HIV-infected subjects was enrolled in the MaxCmin 1 study, the applicant sought to determine whether certain demographic and/or entry criteria were associated with different efficacy outcomes. To this end, the applicant performed a multivariate model analysis to assess the potential influence of a number of study baseline factors on the risk of virological failure (as defined in the MaxCmin 1 protocol) and proportion of subjects with virological suppression at week 48. Factors analyzed included: HIV-RNA $<$ or $\geq$ 400 copies/mL, CD4 cell count, gender, age, HIV transmission factor, geographical region, being naïve to antiretroviral agents, and being naïve to PIs.

In general, the applicant notes that adjustment for such potential confounding factors did not substantially change the unadjusted ratios for comparing outcomes in the IDV/RTV arm to those of the FTV/RTV arm. However, the applicant notes a slightly increased risk (hazard ratio: 2.0 (1.2 – 3.1 univariate), 2.0 (1.3 – 3.3 multivariate)) of virological failure in subjects in the IDV arm in the "switch = failure" analysis. Moreover, the applicant comments that the only baseline variable that consistently showed altered clinical outcome was HIV RNA $\geq$ 400 copies/mL; subjects with such baseline RNA values had an increased risk of virological failure. Furthermore, subjects with prior PI therapy showed a statistically significant increase in the risk for virological non-suppression ("switch included", HIV RNA $>$ 50 copies/mL and "on treatment" HIV RNA $\geq$ 400 copies/mL). However, being experienced or naïve to ART did not independently affect the outcome of the statistical analysis. Lastly, the time until HIV RNA reached $<$400 or $<$50 copies/mL for subjects with baseline HIV RNA values $\geq$ 400 or $>$ 50 copies/mL respectively was not statistically different for subjects in the IDV/RTV arm relative to those in the FTV/RTV arm.

Given the datasets provided by the applicant, no attempt was made to duplicate the applicant's multivariate analysis. Please refer to Dr. Zhou's Statistical Review for further details on the Agency's subanalyses.

D. Efficacy Conclusions

Based on the revised dataset analysis, the FTV/RTV 1000 mg/100 mg BID regimen showed efficacy that was at least comparable to that of the IDV/RTV BID regimen. The virologic response rates of patients in the FTV/RTV arm ranged from [redacted] depending on the use of all or scheduled visits only, LOQ of 50 or 400 copies/mL, and inclusion or exclusion of NASBA assay data from five patients in the efficacy analysis. There are no historical controls that would be appropriate as a comparator of the efficacy of the FTV/RTV BID regimen; clinical studies in support of the initial approval of the

INV and FTV NDAs used antiretroviral regimens that are no longer considered standard of care. Moreover, the response rates shown above may have been affected by the heterogeneous nature of the MaxCmin 1 study population. Many subjects were PI-experienced at entry into the study and close to 40% of entire ITT population bore baseline HIV RNA levels < 400 copies/mL (Table 1).

With regard to the differences in the virologic failure rates between the two treatment arms, those derived from the TLOVR analysis were not as robust as those obtained using the MaxCmin 1 protocol definition of virologic failure. However, in general, the analysis of the MaxCmin 1 study efficacy data by the Division's TLOVR algorithm showed no marked deviations from that performed by the applicant. Please refer to Dr. Zhou's Statistical Review for additional details regarding the Agency's efficacy analysis.

[redacted]. However, the Agency is aware of widespread use of this regimen in clinical practice and inclusion of boosted IDV (with two NRTIs) in the DHHS HIV treatment guidelines as an alternative regimen for initial therapy. But, the use of IDV/RTV has been supplanted by lopinavir/RTV in clinical practice and in the treatment guidelines. Thus, for future studies, a comparator arm consisting of a previously approved RTV-boosted PI regimen will be more useful to determine the efficacy of the proposed SQV combination regimens with RTV. To this end, the applicant has recently presented an abstract on the MaxCmin 2 study, in which the efficacy and safety of FTV/RTV 1000 mg/100 mg BID regimen were compared against those of lopinavir/RTV in a heterogeneous HIV-infected patient population (Youle, et al., 2003). In a preliminary analysis, more patients in the FTV/RTV arm experienced protocol-defined virological failure as compared to those in the comparator arm; such difference was not seen in the on-treatment analysis. Furthermore, more patients in the FTV/RTV arm than those in the lopinavir/RTV arm discontinued the PI regimen due to patient choice. However, the clinical toxicity profile was comparable between the two arms. Whether these results will have significant clinical implications on the use of SQV/RTV combination regimens remains to be seen.

Lastly, since the start of the MaxCmin 1 study, there has been an increased role of genotype/phenotype analysis in guiding the treatment of HIV-infected patients. In many parts of the developed world, resistance testing of HIV strains is performed in many clinical situations, such as prior to start of therapy in treatment-naïve patients and change of antiretroviral regimen in patients who are failing treatment. The MaxCmin 1 study report presents no data on resistance testing, and thus it is unclear whether use of such testing may have altered the virologic, immunologic, or clinical outcomes of the study participants.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

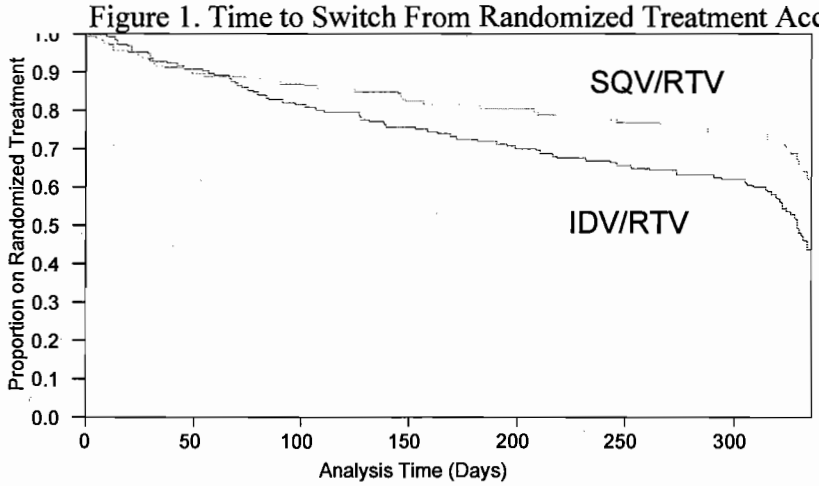
During the 48 week MaxCmin 1 study period, the FTV/RTV 1000 mg/100 mg BID regimen was in general safe and better tolerated than the comparator IDV/RTV BID regimen in the heterogeneous study population of HIV-infected adults with varying treatment histories. The most common adverse events associated with FTV/RTV regimen were gastrointestinal in nature. The number of deaths reported during the course of the study were small and such deaths appeared not to be associated with antiretroviral regimens. With respect to laboratory abnormalities, small but statistically significant increases in bilirubin and creatinine were noted during the study in patients assigned to receive IDV/RTV but not among those randomized to FTV/RTV. Consistent with effects of PIs on lipid profiles, among patients in both arms, small, statistically significant increases in total and LDL cholesterol were noted during the study. The number of patients who withdrew from the randomized treatment due to treatment-limiting adverse events was greater in the IDV/RTV arm than in the FTV/RTV arm.

The safety profile of the patients enrolled in the FTV/RTV arm of the MaxCmin 1 study was in general comparable to previously reported safety profile of unboosted FTV. No new safety issues were identified when RTV was co-administered with FTV in this study. Postmarketing safety data from the applicant as well as the Agency's MedWatch program as summarized in the consultation report from the Office of Drug Safety do not reveal additional safety concerns associated with co-administration of SQV and RTV.

B. Description of Patient Exposure

The applicant's analysis of patient exposure to randomized treatment was confirmed and is shown below:

Figure 1. Time to Switch From Randomized Treatment According to Treatment Arm.



Source: Generated from DISP_DT dataset from applicant, NDA 20828. A similar graph is also shown in NDA 20828 p. 14-55.

Table 7. Number of Subjects on Randomized Treatment During MaxCmin 1 Study.

Week	0	4	12	24	36	48
IDV/RTV	158	151	132	117	105	67
FTV/RTV	148	139	130	121	112	89

Source: NDA 20828 p. 14-55.

The applicant states that at 48 weeks, 202 (66%) of the subjects who started the assigned treatment (ITT) remained on the assigned treatment (59% in IDV/RTV arm and 73% in FTV/RTV arm) (NDA 20828, p. 14-55). However, analysis of the applicant's data by this Medical Reviewer showed that at 48 weeks, 161 out of 306 subjects (52%) were still on assigned treatment (69 out of 158 (43%) in IDV arm and 92 out of 148 (62%) in the SAQ arm). Moreover, as compared to the applicant's Final Study report, the Agency's analysis showed minor differences in the number of subjects on each treatment arm at weeks 0, 4, 8, 12, 24, 36, and 48. Despite these discrepancies, the difference in the number of subjects on each treatment arm during the study was statistically significant (applicant's analysis: log rank test $p = 0.01$; in the Agency's analysis, $p = 0.0084$). Furthermore, the applicant's statement regarding the mean duration of exposure to the study medication (37 weeks in the IDV/RTV arm and 41 weeks in the FTV/RTV arm) was confirmed by this Medical Reviewer.

With regard to patient exposure to study treatments, the applicant also notes that a total of 22 patients in the study reduced the dose of the randomized PI treatment. Specifically, 21 patients who were assigned to the IDV arm reduced the dose of IDV; seven reduced the IDV dose to 600 mg BID (one patient dose reduced further to 400 mg BID) and 14 dose reduced to 400 mg BID (one patient further reduced the dose to 200 mg BID). The applicant states that the median time to first dose reduction was 22 weeks; this value was in accord with that obtained by this Medical Reviewer. In addition, one patient who was randomized to the FTV/RTV arm dose reduced to 800 mg BID after 27 weeks of assigned treatment. Of note, no specific reason for dose reduction was given for any of these 22 subjects. It is assumed by this Medical Officer that this was due to intolerance to the assigned treatment.

C. Methods and Specific Findings of Safety Review

The applicant's analysis of the safety profile of the FTV/RTV BID regimen as compared to that of the IDV/RTV BID regimen was reviewed by the Medical Officer. In particular, the MaxCmin 1 Final Report contains analysis of Grade 3 and 4 adverse events; analysis of Grade 1 and 2 adverse events were not required as per the study protocol. To extend the safety analysis, this Medical Officer used the datasets provided by the applicant to examine Grade 1 and 2 adverse events. In several portions of this section, the Agency's analysis of the datasets and clinical case summaries from the MaxCmin 1 study are shown. The safety profile of the proposed FTV/RTV BID regimen from the MaxCmin 1 study was also compared to previously studied/reported safety profiles of unboosted FTV regimens (studies NV 15355 and NV15182) and that of SQV/RTV regimens containing 400-600 mg RTV (EV 15373). Lastly, postmarketing safety issues associated with co-administration of RTV with SQV and as reported by the applicant and independently

reviewed by the Agency's Office of Drug Safety are summarized in the Appendix of this Clinical Review.

1. Overview of Safety Analysis-MaxCmin 1 study.

The MaxCmin 1 protocol provided the following definitions. An adverse event (AE) was defined as any untoward medical occurrence in a subject administered a pharmaceutical product which did not necessarily have a causal relationship with this treatment. Treatment-limiting AEs were defined as AEs sufficiently severe for the subject to prematurely switch from the assigned PI treatment. A serious adverse event (SAE) was defined as any event that was: fatal; life threatening (except if clearly related to HIV disease); potentially at immediate risk of death; disabling or incapacitating; a congenital anomaly; an event which may have jeopardized the subject or required intervention to prevent one of the outcomes listed in the points above (except if clearly related to HIV disease); and/or required inpatient hospitalization or prolonged a current hospitalization. As described in the MaxCmin 1 study protocol, laboratory analyses (including CD4 cell count and HIV-1 viral loads), and screening for AEs were performed at study visits at weeks 4, 12, 24, 36 and 48.

The applicant provided tabulation of AEs by treatment group, intensity (ACTG grading scale), relationship to randomized treatment (not related, remotely/unlikely, possibly, probably/likely, definitely related), and by seriousness (i.e. AE or SAE). The applicant also provided clinical summaries for all AEs that led to premature switch from the randomized treatment as well as for all SAEs. Furthermore, the time to development of a grade 3 or 4 AE according to treatment arm was analyzed using a Kaplan-Meier plot. Moreover, laboratory markers during the study were analyzed for statistically significant changes from baseline and the incidence of marked laboratory test value abnormalities. Finally, the applicant provided brief description of deaths and one pregnancy that occurred during the study. The data described above were analyzed by the Clinical and Statistical Reviewers.

2. Grades 1/2 Adverse Events-MaxCmin 1 study.

The applicant did not provide a detailed analysis of Grade 1 and 2 AEs. For the Agency's safety analysis, datasets provided by the applicant were used to identify Grades 1/2 AEs (all causality and at least possibly related to treatment). Such analysis was performed since differences in the types and/or incidence of Grade 1 and 2 AEs may, over the course of long-term treatment, affect tolerability and/or adherence to antiretroviral therapy.

Table 8. Summary of Adverse Events (Grades 1/2) All Causality, ≥ 2% of patients in Each Arm.

	IDV/RTV	FTV/RTV
All Body Systems		
Total number of patients with at least one Grade 1/2 AE	146/158 (92%)	119/148 (80%)

Total number of Grade 1/2 AEs	710	490
Gastrointestinal		
Diarrhea	33 (21%)	35 (24%)
Nausea	38 (24%)	27 (18%)
Vomiting	25 (16%)	19 (13%)
Abdominal pain	17 (11%)	21 (14%)
Flatulence		7 (5%)
Bloating		7 (5%)
Dyspepsia/Gastritis	3 (2%)	6 (4%)
Throat Pain		4 (3%)
Constipation	3 (2%)	4 (3%)
Candida stomatitis	7 (4%)	
Gingivitis	3 (2%)	
Dermatological		
Rash/dermatitis	39 (25%)	20 (14%)
Pruritis	8 (5%)	3 (2%)
Dry skin	22 (14%)	8 (5%)
Herpes simplex	3 (2%)	
Respiratory		
Pneumonia	7 (4%)	8 (5%)
Cough	5 (3%)	4 (3%)
Dyspnea		3 (2%)
Bronchospasm	3 (2%)	
Bronchitis	4 (3%)	4 (3%)
Sinusitis		4 (3%)
Influenza		6 (4%)
Neurological		
Headaches	12 (8%)	9 (6%)
Neuropathy/Paresthesia	7 (4%)	8 (5%)
Dizziness	10 (6%)	5 (3%)
Insomnia	5 (3%)	
Body as a Whole		
Fatigue	23 (15%)	17 (11%)
Fever	5 (3%)	9 (6%)
Lipodystrophy	12 (8%)	9 (6%)
Weight loss	5 (3%)	4 (3%)
Musculoskeletal pain	21 (13%)	11 (7%)
Hair loss	17 (11%)	
Hematological		
Anemia	5 (3%)	7 (5%)
Thrombocytopenia	3 (2%)	
Elevated Laboratory Tests		
Elevated ALT	5 (3%)	8 (5%)
Elevated AST	3 (2%)	5 (3%)
Elevated bilirubin	19 (12%)	5 (3%)
Elevated Alkaline phosphatase		6 (4%)
Elevated amylase	3 (2%)	4 (3%)
Hypertriglyceridemia	10 (6%)	5 (3%)
Hypercholesterolemia	6 (4%)	5 (3%)
Increased creatinine	3 (2%)	
Renal		
Renal colic	4 (3%)	
Kidney stone	4 (3%)	
Urinary Tract Infection	4 (3%)	
Hematuria	9 (6%)	

Source: NDA 20828 AE.xpt dataset; Agency analysis

Table 9. Summary of Adverse Events (Grades 1/2) at Least Possibly Related, ≥ 2% of Patients in Each Arm.

	IDV/RTV	FTV/RTV
All Body Systems		
Total number of patients with at least one Grade 1/2 AE	131/158 (83%)	91/148 (61%)
Total number of Grade 1/2 AEs	435	244
Gastrointestinal		
Diarrhea	23 (15%)	29 (20%)
Nausea	29 (18%)	22 (15%)
Vomiting	18 (11%)	13 (9%)
Abdominal pain	14 (9%)	14 (9%)
Flatulence		7 (5%)
Bloating		5 (3%)
Dyspepsia/Gastritis	3 (2%)	3 (2%)
Constipation		3 (2%)
Altered taste in mouth	3 (2%)	
Dermatological		
Rash/dermatitis	32 (20%)	9 (6%)
Pruritis	7 (4%)	3 (2%)
Dry skin	22 (14%)	7 (5%)
Neurological		
Headaches	8 (5%)	4 (3%)
Neuropathy/Paresthesia	5 (3%)	5 (3%)
Dizziness	6 (4%)	
Insomnia	3 (2%)	
Body as a Whole		
Fatigue	18 (11%)	13 (9%)
Lipodystrophy	12 (8%)	8 (5%)
Weight loss	3 (2%)	
Musculoskeletal pain	9 (6%)	
Hair loss	15 (9%)	
Hematological		
Anemia	3 (2%)	
Elevated Laboratory Tests		
Elevated ALT	4 (3%)	5 (3%)
Elevated AST		5 (3%)
Elevated bilirubin	19 (12%)	5 (3%)
Elevated alkaline phosphatase		7 (5%)
Hypertriglyceridemia	10 (6%)	5 (3%)
Hypercholesterolemia	6 (4%)	4 (3%)
Increased creatinine	3 (2%)	
Renal		
Renal colic	4 (3%)	
Kidney stone	4 (3%)	
Hematuria	8 (5%)	

Source: NDA 20828 AE.xpt dataset; Agency analysis.

In both tables shown above, it is evident that the majority of patients in each arm of the MaxCmin 1 study experienced Grade 1/2 AEs of all causality (92% in IDV/RTV arm, 80% in FTV/RTV arm) and at least possibly treatment-related (83% vs. 61%, respectively). In addition, among patients randomized to the IDV/RTV arm, there are greater incidences of hyperbilirubinemia as well as dermatological (including hair loss,

dry skin, and dermatitis/rash) and renal AEs as compared to participants in the FTV/RTV arm; these AEs have previously been reported with IDV use.

With respect to Grade 1/2 AEs seen in the FTV/RTV arm, the predominant body system that was affected by this regimen was gastrointestinal. Again, such AEs as nausea, vomiting and diarrhea have been well documented in clinical practice as well as in previous clinical studies with FTV. Lastly, it is noted that patients in the FTV/RTV arm experienced far fewer Grade 1/2 AEs (all causality: 498, at least possibly treatment-related: 248) as compared to those in the IDV/RTV arm (713 and 436, respectively).

3. Grade 3 and 4 Adverse Events-MaxCmin 1 study

The applicant notes that a total of 188 AEs of Grade 3 and/or 4 were reported in 100 study subjects (65 in IDV/RTV arm, 35 in FTV/RTV arm), of which 106 events (in 46 patients in IDV/RTV arm, 19 patients in FTV/RTV arm) were assessed as being at least possibly related to the study medication. The applicant notes that the difference in the numbers of patients in the IDV/RTV arm who experienced Grade 3/4 AE (all causality and those related to treatment) and those in the FTV/RTV arm was statistically significant ($p = 0.0015$ and 0.007, respectively).

In the Agency's analysis of the data, 183 events were identified in 100 subjects (117 events in 65 patients in IDV/RTV arm, 66 events in 35 patients in FTV/RTV arm). Of these events, 105 were at least possibly related to the study medication (69 events in 47 patients in IDV/RTV arm, 36 events in 19 patients in FTV/RTV arm). These numbers are similar to those provided by the applicant and do not significantly affect the statistical significance of the differences between the treatment arms.

Table 10. Summary of Adverse Events (Grades 3/4), All Causality, at Least ≥ 2% of Patients.

	IDV/RTV	FTV/RTV
All Body Systems		
Total number of patients with at least one Grade 3/4 AE	65 (41%)	35 (24%)
Total number of Grade 3/4 AEs	117	66
Gastrointestinal		
Nausea	4 (3%)	6 (4%)
Vomiting	5 (3%)	3 (2%)
Abdominal pain	5 (3%)	
Dermatological		
Dry skin	3 (2%)	
Neurological		
Depression	4 (3%)	
Body as a Whole		
Fatigue		3 (2%)
Lipodystrophy	3 (2%)	
Fever	3 (2%)	
Hair loss	3 (2%)	
Hematological		
Anemia		3 (2%)
Thrombocytopenia		3 (2%)

Elevated Laboratory Tests		
Elevated ALT	3 (2%)	
Elevated AST	3 (2%)	
Elevated bilirubin	4 (3%)	
Hypertriglyceridemia	8 (5%)	
Renal		
Kidney stone	7 (4%)	

Source: NDA 20828 AE.xpt dataset; Agency analysis.

Table 11. Summary of Adverse Events (Grade 3/4) at Least Possibly Related, ≥ 2% of Patients.

	IDV/RTV	FTV/RTV
All Body Systems		
Total number of patients with at least one Grade 3/4 AE	47 (30%)	19 (13%)
Total number of Grade 3/4 AEs	69	36
Gastrointestinal		
Nausea	4 (3%)	6 (4%)
Vomiting	5 (3%)	3 (3%)
Abdominal pain	3 (2%)	
Dermatological		
Dry skin	3 (2%)	
Body as a Whole		
Fatigue		3 (2%)
Lipodystrophy	3 (2%)	
Hair loss	4 (3%)	
Elevated Laboratory Tests		
Elevated bilirubin	4 (3%)	
Hypertriglyceridemia	8 (5%)	
Renal		
Kidney stone	7 (4%)	

Source: NDA 20828 AE.xpt dataset; Agency analysis.

Given these data, the following comments may be made. First, the patients in the IDV/RTV arm experienced more AEs than those in the FTV/RTV arm. Second, the numbers of Grade 3/4 AEs related to the gastrointestinal system were similar in both arms of the study. Third, renal complications and hyperbilirubinemia were noted with patients on IDV/RTV, as was previously discussed with Grade 1/2 AEs. Fourth, for each organ system that was affected by these AEs, relatively small, qualitative differences in the number of observed Grade 3/4 AEs were noted between the two arms. However, given the small patient population and number of AEs observed, no statistical tests were performed on such differences.

With regard to time to development of a grade 3 or 4 AE during the MaxCmin 1 study, the applicant performed a Kaplan-Meier survival estimate analysis. The applicant reports that the risk of developing at least one grade 3 or 4 AE was higher for patients on IDV/RTV than those in the FTV/RTV arm (log rank test: $p = 0.002$). Similar numbers were obtained by the Agency's analysis. A statistically significant difference in the time-to-event (all causality and at least possibly treatment related)-free survival was seen between FTV/RTV and IDV/RTV (all causality: $p = 0.0081$; at least possibly treatment-related: $p=0.0004$) (Dr. Zhou, Statistical Reviewer).

4. Serious Adverse Events-MaxCmin 1 study

The applicant noted 72 total SAEs in 50 patients (37 events in 27 patients in IDV/RTV arm, 35 events in 23 patients in the FTV/RTV arm). Of these, 15 events in 14 subjects in the IDV/RTV arm and one event in one patient in the FTV/RTV arm were deemed as being at least possibly related to trial medication. The difference between the number of patients experiencing SAEs in the IDV/RTV arm and those in the FTV/RTV arm was statistically significant ($p = 0.0012$).

The applicant has provided case summaries of all SAEs from the MaxCmin 1 study. For the Agency's analysis, each of the 74 SAE case summaries were reviewed by this Medical Officer. In all, 38 SAEs in 27 patients in IDV/RTV arm and 36 SAEs in 24 patients in the FTV/RTV arm) were noted. Of these, 15 events in 14 subjects in the IDV arm and one event in one patient in the FTV/RTV arm were considered to be at least possibly related to trial medication by the study investigators. Of the IDV/RTV associated SAEs, eight events were related to the renal system (renal insufficiency:1; renal failure/increased creatinine:2; renal colic:2; and nephrolithiasis:3). The single SAE in the FTV/RTV arm was a subject who experienced grand mal seizures. However, a review of deaths that occurred in this study suggest that the possibility of a relationship between the study medications (including FTV/RTV) and liver failure in patient #2003105 cannot be excluded (see Deaths, below); on the SAE forms, the liver failure and death of this patient is listed as "no relationship" to study medications. From these findings, it appears that: 1) there were significantly greater number of SAEs observed among the IDV/RTV patient population than the FTV/RTV patients; 2) among the IDV/RTV study subjects, the organ systems affected with SAEs were again consistent with those associated with previously reported AEs for IDV; and 3) the possibility that study medications were at least possibly related to the liver failure and death of patient # 2003105 cannot be excluded.

5. Clinical AEs Leading to Switch from Randomized Treatment-MaxCmin 1 study

The initial Patient Disposition table in the MaxCmin 1 study report was revised by the applicant according to the Division's TLOVR analysis algorithm. The updated Patient Disposition table is presented in the Integrated Review of Efficacy (Table 5). There is a slight difference in the number of subjects that switched treatment because of treatment-limiting non-fatal AE (67 as stated in the Final Report, 68 as provided in Table 5). However, this minor difference does not significantly affect the difference in the number of such patients in the IDV/RTV arm (45) as compared to those in the FTV/RTV arm (22) ($p = 0.006$, Fisher's exact test per applicant). The 67 case summaries for the clinical non-fatal AEs that led to treatment withdrawal were reviewed by this Medical Officer.

The applicant notes that the clinical non-fatal AEs leading to withdrawal from assigned therapy were primarily gastrointestinal and renal in nature. Eleven subjects (6%) randomized to IDV/RTV but none in the FTV/RTV arm switched from assigned therapy

due to renal toxicity. In both treatment arms, about 10% of the subjects discontinued assigned therapy due to gastrointestinal toxicity. Out of the 67 subjects who withdrew from assigned treatment, 45 (67%) experienced AEs of grades 1 or 2. As shown in Table 12, these 67 AEs were then analyzed by the applicant with respect to the affected body system, treatment arm, and AE grade. Similar analysis by this Medical Officer did not reveal significant differences between the Agency's review of these AEs and that of the applicant.

Table 12. Number of Subjects with Clinical Non-Fatal AEs Leading to Permanent Switch from Randomized Treatment According to Treatment Arm.

Number of subjects With event	IDV/RTV	FTV/RTV
Nervous system	2	4
Renal	11	0
Pulmonary	0	0
Gastrointestinal	17	13
Skin/Hair	10	1
Fatigue/fever	2	0
Other	3	2

AE subsets: Grade 1: 14, Grade 2: 30, Grade 3: 20, Grade 4: 3
p-value for this difference in distribution among those who permanently switched from randomized treatment: 0.02 (Fisher's exact test)
Source: Adapted from Table 8, NDA 20828, p. 14-61.

Of these events, gastrointestinal, skin/hair, and renal events were analyzed further by this Medical Officer:

Table 13. Agency's Subanalysis of Clinical Non-Fatal AEs Leading to Permanent Switch from Randomized Treatment According to Treatment Arm.

AE	IDV/RTV	FTV/RTV
Renal		
Renal colic/flank pain	3	0
Nephrolithiasis	6	0
Renal failure	1	0
Renal Insufficiency	1	0
Gastrointestinal		
Diarrhea	6	2
Nausea	4	1
Meteorism	0	2
Vomiting	6	5
Abdominal pain	0	1
Nonspecific	1	1
Skin/hair		
Pruritis	2	1
Allergic rash	3	0
Retinoid syndrome	1	0
Alopecia	3	0

Source: Agency's review of treatment-limiting AE case summaries, NDA 20828, pp. 15-43 to 15-52.

Thus, patients enrolled in the IDV/RTV arm experienced a greater number of renal and dermatological AEs that led to switching of study-assigned antiretroviral therapy than those in the FTV/RTV arm. In contrast, patients in the FTV/RTV arm who switched the assigned therapy due to AEs did so predominantly due to gastrointestinal AEs. These observations are consistent with the previously discussed AE profiles of patients in the IDV/RTV and FTV/RTV arms.

6. Deaths-MaxCmin 1 Study

The applicant reports that three subjects who died after starting the randomized treatment, as well as one that died after randomization but before being notified of the results of the randomization and the Baseline visit. Two of these subjects were naïve to antiretroviral treatment at the time of enrollment into the study and that both had experienced AIDS-defining events (Kaposi's sarcoma (KS) and *Pneumocystis carinii* 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 time of study entry.

The summaries of the SAEs and the CRFs for these subjects were reviewed by this Medical Officer. The clinical descriptions of each of these subjects are summarized below. Note that patients 5 and 6 were not included in the Final Report as deaths that occurred during the study. These patients participated in the study, but 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 100mg 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, 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 bilirubin:138 (μmol/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 patient who was randomized to the FTV/RTV arm but did not yet start the assigned treatment was found dead at his residence. An autopsy revealed an old coronary thrombosis, a "weakened heart" due to the previous 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 only palliative care was given 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; no other data were presented for this patient. Aside from patient #3, there appears to be no evidence that the study-related antiretroviral therapy of other five patients directly contributed to the deaths.

7. Laboratory Parameters-MaxCmin 1 study

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. The HIV-1 RNA and CD4+

lymphocyte count analyses have been discussed in the Integrated Review of Efficacy section of this Clinical Review as well as in the Statistical Review by Dr. Susan Zhou. All measurements were transformed into SI units prior to data analysis except for platelets, WBC count, and lymphocytes (all in 10^9/L).

With respect to the analysis of laboratory data, 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. Moreover, 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. Such an approach would likely limit the full evaluation of liver function during the course of the study.

7a. Hematologic, pancreatic, renal and liver-related laboratory markers

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 notes the following: 1) in both treatment arms over the 48 week study period, the hemoglobin level remained unaffected while the WBC, lymphocyte counts, and the platelet counts increased by a median of 8-13%; 2) the creatinine increased by 2-4% whereas the amylase and the AST/ALT tended to decline in both arms without a consistent pattern; and 3) the bilirubin level increased in subjects on IDV/RTV with a peak at week 4 (median increase 115%; 45% had bilirubin > 22 µmol/L); during the duration of the study, 71% of subjects in the IDV/RTV arm had at least one bilirubin level > 22 µmol/L, whereas no median change in bilirubin levels was observed in FTV/RTV arm at week 48.

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 14. Mean Absolute Values for Hematologic, Pancreatic, Renal, and Liver-related Laboratory Markers According to Treatment Arm.

Lab parameters	IDV baseline	IDV Week 4	IDV Week 12	IDV Week 24	IDV Week 36	IDV Week 48	FTV baseline	FTV week 4	FTV week 12	FTV week 24	FTV week 36	FTV week 48
Hemoglobin (mmol/L)	8.41	8.29	8.28	8.44	8.44	8.5	8.47	8.38	8.47	8.6	8.6	8.7

WBC (10^9/L)	5	5.5	5.62	5.92	6.1	6.17	5.44	5.75	5.82	5.87	6.15	6
Platelets (10^9/L)	218	234	245	248	249	248	209	230	231	232	228	233
Lymphocytes (10^9/L)	1.71	1.81	1.8	1.85	1.87	1.94	1.75	1.92	1.86	1.91	1.87	1.94
Amylase (IU/L)	117	119	112	121	122	121	118	121	116	116	115	113
Creatinine (µmol/L)	79	85.6	85.4	86.3	87.6	85.2	83	86.3	86.4	83.8	85.4	84.7
Bilirubin (µmol/L)	12.3	23.9	22.5	22.1	19.6	17.8	13.7	11.9	12.2	13.1	12.9	12.4
AST (IU/L)	34.9	33	36.2	37.3	35.1	34.3	39.3	38.6	36.1	32.5	35.6	36.4
ALT (IU/L)	37.2	30	36	29.5	34	30	41.3	42.9	35.4	32.8	34.3	37.8

Source: LABP.xpt dataset for NDA 20828.

For each of these laboratory parameters, the statistical significance of change from baseline values and % 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. The Agency's analysis revealed that between the treatment arms: 1) with respect to bilirubin, the changes from baseline and % change from baseline were statistically significant for all time windows ($p < 0.0001$); and 2) with respect to creatinine, the change from baseline was statistically significant at weeks 24 ($p = 0.02$) and week 36 ($p < 0.0001$), and % change from baseline were statistically significant at week 24 ($p = 0.01$), week 36 ($p < 0.0001$) and week 48 ($p = 0.05$). No statistically significant changes in either changes from baseline values or % change from baseline were noted for other laboratory parameters.

Thus, with respect to bilirubin and creatinine values obtained at specific points during the study, the change from baseline values and % change from baseline values from patients receiving IDV/RTV were greater than the corresponding values from patients in the FTV/RTV arm. The persistently elevated bilirubin levels in patients assigned to the IDV/RTV arm is consistent with the hyperbilirubinemia that has been well described to be associated with IDV use. Also, the statistical analysis of creatinine values is consistent with renal AEs and SAEs seen much more frequently in the IDV/RTV arm during the study. It is possible that the statistically significant changes in creatinine values at other time points during the study may have been present but were not evident due to the applicant's extension of each time point window. Similarly, 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.

7b. Lipid parameters

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 15. Median % and Absolute Change from Baseline to Weeks 4 and 48 for the Three Lipid Parameters (in mmol/L) According to Treatment Arm.

	IDV/RTV			FTV/RTV			
	Number of patients with lab values drawn at baseline (N)	Week 4 Change from Baseline (IQR) (N)	Week 48 Change from Baseline (IQR) (N)	Number of patients with lab values drawn at baseline (N)	Week 4 Change from Baseline (IQR) (N)	Week 48 Change from Baseline (IQR) (N)	P value for the Treatment effect At week 4/48
Cholesterol Median % change	162	17% (2-32) N=147	17% (0-41) N=135	145	9% (-4–20) N=135	9% (-7-25) N=131	0.005/0.01
LDL Median % change	99	21% (0-48) N=103	19% (0-54) N=89	94	6% (-11-21) N=96	3% (-12-29) N=75	0.0003/0.04
TG Median % change	148	29% (-6-80) N=153	23% (-20-97) N=138	150	13% (-16-68) N=137	9% (-34-41) N=135	0.03/0.01
Cholesterol Absolute change (mmol/L)	n/a	0.8 (0.1-1.3)	0.8 (0.0-1.8)	n/a	0.4 (-0.2-0.9)	0.4 (-0.4-1.1)	0.002/0.005
LDL Absolute change (mmol/L)	n/a	0.6 (0.0-1.2)	0.5 (0.0-1.2)	n/a	0.2 (-0.3-0.6)	0.1 (-0.5-0.9)	0.0004/0.03
TG Absolute change (mmol/L)	n/a	0.4 (-0.1-1.2)	0.3 (-0.3-1.0)	n/a	0.1 (-0.3-0.8)	0.1 (-0.7-0.8)	0.03/0.03

Source: NDA 20828, adapted from p. 14-63.

From these data, the applicant makes the following observations: 1) 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; 2) the elevation of lipids was consistently more pronounced for subjects randomized to the IDV arm as compared to subjects in the SQV arm; 3) this difference was significant for all measurements at all visits except the LDL-cholesterol changes at week 48.

The Agency's analysis of lipid parameters differs 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 (Dr. Zhou, Statistics Reviewer). 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. For the two treatment arms, the number of patients who had lipid levels drawn at baseline and at four and 48 weeks are shown in Table 15. Thus, the statistical significance of the differences in LDL and total cholesterol levels between the treatment arms may be tempered by the fact that sampling of lipid profiles was somewhat limited during the course of the study.

7c. Marked Laboratory Test Value Abnormalities

The applicant has provided a table showing the proportion of subjects with abnormal values of the laboratory parameters discussed in the two previous sections. This table is shown below:

Table 16. 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.

	IDV/RTV Baseline	IDV/RTV Week 4	IDV/RTV Week 48	FTV/RTV Baseline	FTV/RTV Week 4	FTV/RTV Week 48
Hemoglobin (< 7 mmol/L)	8	10	6	10	13	4
WBC count (< 3 x 10^9/L)	15	4	1	5	6	3
Platelet count (<150 x 10^9/L)	14	9	5	18	12	11
Lymphocyte Count (0.7 x 10^9/L)	11	6	3	11	5	5
Amylase (> 300 U/L)	3	4	3	3	4	2
Creatinine (130 µmol/L)	1	1	1	1	1	2
Bilirubin (22 µmol/L)	9	43	23	13	6	7
AST (>40 U/L)	25	20	22	21	20	19
ALT (>40 U/L)	31	20	16	30	30	26
Cholesterol (6.2 mmol/L)	16	26	36	18	27	27
LDL Cholesterol (> 3.2 mmol/L)	48	60	60	50	56	62
Triglycerides (> 2.3 mmol/L)	26	41	38	30	36	32

Source: NDA 20828 p. 14-64.

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.

With respect to the numbers shown in this table, the Agency's analysis showed no significant changes/discrepancies with those of the applicant. Overall, there is no striking

difference between the incidences of abnormal laboratory values between the two treatment arms except for bilirubin levels that were seen in greater numbers in the IDV/RTV arm. In both groups, there were similar percentages of patients with elevated transaminases and lipid profiles.

8. Pregnancy-MaxCmin 1 study

During the MaxCmin 1 study, the applicant noted one case of pregnancy. Subject # 1503120, a 25 year old, black woman of African origin and who became infected with HIV through heterosexual contact, was found to be pregnant with her HIV-negative partner after about 45 weeks of follow-up in the study. This patient was PI-experienced but had adherence problems with antiretroviral regimens and had an HIV viral load < 50 copies/mL at baseline. The patient was assigned to the IDV/RTV arm with concomitant administration of stavudine and lamivudine. After an episode of renal insufficiency, all antiretroviral treatment was stopped at 11 weeks of follow-up and was restarted at week 13 of the study with substitution of abacavir for IDV/RTV. When the subject was found to be pregnant, stavudine was replaced with zidovudine and abacavir with nelfinavir (later switched back to abacavir 19 weeks later). At 30 weeks gestation, because of pre-eclampsia, the subject gave birth via Caesarian section to a live baby. With regard to the newborn, no congenital or other abnormalities were reported. The baby received post-partum treatment with zidovudine for 37 days; the HIV status of the newborn is not known to the applicant at the time of the study Final Report.

Since there were no cases of pregnancy in the FTV/RTV arm, no comments may be made at this time regarding the possible effects of this PI combination regimen on the mother and/or the child during pregnancy.

9. Safety Analysis – EPIMED 1 study

In the EPIMED 1 study, a total of ten patients reported a total of 18 AEs; four patients in Group A (FTV/RTV then INV/RTV) reported seven events and six patients in Group B (INV/RTV then FTV/RTV) reported 11 events.

Table 17. Summary of Adverse Events by Body System – EPIMED I Study.

Body system/ Adverse event	Group A N = 12 # (severity, relationship to treatment)	Group B N = 12 # (severity, relationship to treatment)
Gastrointestinal system	3	7
Constipation	1 (mild, possible relationship)	0
Meteorism	1 (mild, possible relationship)	1 (moderate, probable relationship)
Heartburn	1 (mild, questionable relationship)	0
Abdominal symptoms	0	2 (moderate, probable; moderate, possible)
Diarrhea	0	3 (2 moderate, possible; 1 mild, possible)
Stomach pain	0	1 (moderate, possible relationship)
Central nervous system	0	1
Dizziness/vertigo	0	1 (mild, questionable)
Respiratory system	1	0
Bronchitis	1 (mild, unrelated)	0

Other	3	3
Fever	1 (mild, questionable)	1 (moderate, no relationship)
Fatigue	1 (mild, questionable)	1 (mild, questionable)
Oral herpes simplex	1 (mild, no relationship)	0
Tonsillitis	0	1 (severe, no relationship)

Source: NDA 20828, p. 4-94.

The individual patient AE listing that was provided by the applicant was reviewed by this Medical Officer and confirms the figures presented in Table 17. There were no deaths or SAEs that were reported during the study, and none of the AEs led to the withdrawal of patients from the study.

As specified in the EPIMED 1 protocol, lipid profiles (fasting and non-fasting triglyceride and total cholesterol values) and AST, ALT, and GGT values were measured in each patient on day 0 and day 10 of the study. These values were provided by the applicant and reviewed by this Medical Officer. There are isolated laboratory values that are outside of the normal range, However, the applicant concludes that there did not appear to be any major shifts in laboratory parameters that occurred during the study period. The Agency's safety review agrees with the applicant's analysis. The one patient (B11) who took rifabutin during the course of study did not experience significant abnormalities in the liver function tests.

D. Adequacy of Safety Testing

With regard to the MaxCmin 1 study, the range of laboratory parameters that were examined as well as frequency of monitoring for AEs and laboratory tests appear adequate. The potential limitations of analysis due to the extended study windows and monitoring of one transaminase (either AST or ALT) during study visits have been previously discussed.

Given the primary nature of the EPIMED 1 as a PK study and the relatively short duration of the study drug regimens, it appears that the scope of safety and laboratory monitoring was appropriate for this study.

E. Summary of Critical Safety Findings and Limitations of Data

As described in detail above, data from the MaxCmin 1 study suggest that the safety profile of the FTV/RTV BID regimen is more favorable as compared to that of the IDV/RTV BID regimen. As compared to the patient population in the IDV/RTV arm, there were fewer patients in the FTV/RTV arm who experienced adverse events (at least possibly related to treatment, all grades, AE and SAEs, and treatment-limiting AEs). With respect to laboratory parameters, small, statistically significant increases in LDL and total cholesterol values were seen in both treatment arms. Furthermore, small, statistically significant increases during the study were seen in the creatinine and bilirubin values among patients in the IDV/RTV arm but not in the FTV/RTV arm. Lastly, there were no qualitatively apparent differences in the number of patients in both arms of the

study that developed marked laboratory test value abnormalities. No treatment-related deaths and complications of pregnancy were reported.

The safety profile of IDV/RTV as seen in the MaxCmin 1 study is similar to that observed for IDV/RTV regimens in the recently published BEST study. In the BEST study (Arnaiz, et al., 2003), the efficacy and safety during 48 week treatment of IDV 800 mg TID + two NRTIs was compared against IDV 800 mg BID (liquid form) / RTV 100 mg BID + 2 NRTIs in HIV-1 infected patients. In this study, 30 % (47 out of 161) of patients in the IDV/RTV BID regimen switched therapy due to AEs. Moreover, genitourinary/renal Grade 3/4 AEs were seen in 20% (33 out of 161) of patients and were treatment-limiting in 15 patients. It is possible that the formulations of IDV used in the BEST study may have had altered the PK profile of IDV and thus may have modified the patient exposure and adverse event profile.

The safety profile of FTV/RTV BID regimen as shown in the MaxCmin 1 study is comparable to that observed in previous studies using FTV in the absence of RTV. There were no substantial differences in the frequency and types of AEs observed in the FTV/RTV arm of the MaxCmin 1 study and those seen in studies NV 15355 (48 week) and NV 15182 (24 and 48 week safety data reviewed in 1997; 60 week final safety report summarized in the Appendix of this Clinical Review). Of note, when used in BID combination regimens with INV, higher doses (400-600 mg BID) of RTV led to increased incidence of circumoral and peripheral paresthesias and taste perversion as well as greater incidence of abnormal LFTs (study EV 15373, reviewed by the Division in 1999). At the RTV doses used in the MaxCmin 1 study, no increased incidence of such events (likely associated with higher doses of RTV) was seen in the FTV/RTV arm.

The evaluation of the safety profile of FTV/RTV in the MaxCmin 1 study is limited by: 1) the lack of documented quality control of AE datasets and ICD 10 coding of AEs, and 2) extension of study time point windows beyond those specified in the protocol (and thus may confound the time-dependent changes of laboratory variables);

To expand the focus of safety analysis for the proposed SQV/RTV combination regimens, AEs that have previously been reported to the applicant and the Agency's MedWatch database regarding combination dosing of RTV with SQV were reviewed. As detailed in the Appendix of this Clinical Review, no new AEs were noted when SQV and RTV were co-administered. In general, gastrointestinal events associated with SQV use as well as clinical and laboratory abnormalities associated with RTV use (paresthesia, taste perversion, elevated lipid profile) and AEs associated with antiretroviral use in general (e.g. lipodystrophy) were noted.

VIII. Dosing, Regimen, and Administration Issues

The proposed FTV/RTV and INV/RTV combination dosing regimens provides patient exposure to SQV that is at least equal to that of the approved FTV 1200 mg TID regimen. Moreover, given the relatively poor bioavailability of SQV following INV dosing, INV

should no longer be dosed as the sole PI but instead be given as 1000 mg with 100 mg of RTV BID. The proposed regimens will likely require additional PK studies in certain patient populations, especially those with moderate to severe liver dysfunction. Furthermore, a formal test of the safety and efficacy of the SQV/RTV BID regimens should be performed as a clinical study in HIV infected adults. In such studies, a comparator regimen should contain another RTV-boosted PI.

IX. Use in Special Populations

A. Evaluation of applicant's Gender Effects Analyses and Adequacy of Investigation

In the MaxCmin 1 study, 22% of the ITT subjects were female. The applicant's univariate and multivariate analyses of the MaxCmin 1 efficacy data did not identify gender-specific effects on the incidence of protocol-defined virological failures. Please refer to Dr. Zhou's Statistical Review for details on the Agency's analysis.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

As above, the applicant's statistical analyses of the MaxCmin 1 efficacy data did not identify age- or geographical region-specific effects on the incidence of protocol-defined virological failures. The applicant provides no evidence suggesting that similar analyses were performed regarding race or ethnicity. Again, please refer to Dr. Zhou's Statistical Review for details on the Agency's analysis.

[ ]

D. Comments on Data Available or Needed in Other Populations

As discussed above, the proposed regimen should be examined in specific patient populations, including those with moderate to severe liver dysfunction and pediatric patients.

X. Conclusions and Recommendations

A. Conclusions

Based on the PK data from the EPIMED 1 study, SQV exposures generated from both combination BID regimens were at least equivalent to that of the currently approved and recommended FTV dosing regimen (1200 mg TID). In addition, as shown in the MaxCmin 1 study, the safety profile of the FTV/RTV 1000 mg/100 mg BID regimen is comparable to that of the unboosted FTV 1200 mg TID regimen. In principle, the addition of low dose RTV to the FTV dosing regimen will expose patients to risk of developing RTV-associated adverse events. However, with adequate drug-drug interaction studies and labeling changes, such risk is expected to be significantly outweighed by the benefits of increased SQV exposure and lowered pill burden.

The efficacy of the FTV/RTV BID regimen as demonstrated in the MaxCmin 1 study is within the range expected for administration of a new PI regimen among HIV infected patients with varying treatment histories. But, the comparator PI combination regimen that was used in the MaxCmin 1 study has not been approved by the Agency for treatment of HIV infection. A more rigorous testing of the proposed SQV/RTV combination regimens would involve a clinical study using an approved RTV-boosted PI regimen as the comparator.

Based on clinical experience with INV and results of the EPIMED 1 study, SQV exposure and the adverse event profile of twice-daily INV/RTV regimen are not expected to be significantly different from those of the FTV/RTV regimen. The addition of RTV to the FTV and INV product labels require significant changes, most notably drug-drug interactions associated with RTV.

Of note, the applicant had originally proposed to include PK data from once-daily administration of FTV 1600 mg in combination with RTV 100 mg. However, the SQV C_{min} that is generated from such a regimen is variable and the lower limit of its 95% confidence interval falls significantly below the corresponding C_{min} confidence interval limits derived from twice-daily INV/RTV and FTV/RTV regimens. Thus, the information submitted in these NDAs do not adequately support the inclusion of PK data from once-daily administration of FTV and RTV in the INV and FTV package inserts.

B. Recommendations

Evidence provided in these supplemental NDAs appear sufficient to recommend approval of the proposed 1000 mg/100 mg BID combination regimens of FTV/RTV and INV/RTV. A number of changes to the FTV and INV product labels are proposed,

particularly regarding drug-drug interactions (please see Dr. DiGiacinto's Biopharmaceutics Review for details). In addition, to better describe the potential risk for hyperlipidemia and/or pancreatitis as previously included in the RTV label, the following paragraph is proposed for inclusion into the two product labels:

> Elevated cholesterol and/or triglyceride levels have been observed in some patients taking saquinavir in combination with ritonavir. Marked elevation in triglyceride levels is a risk factor for development of pancreatitis. Cholesterol and triglyceride levels should be monitored prior to initiating combination dosing regimen of FORTOVASE or INVIRASE with ritonavir, and at periodic intervals while on such therapy. In these patients, lipid disorders should be managed as clinically appropriate.

Furthermore, in the Indications and Usage section of the two labels, inclusion of the following sentence is proposed to the applicant:

[ ]

Moreover, the following paragraphs are proposed for the use of SQV in the pediatric population in the FTV and INV package inserts:

[ ]

Lastly, the dosing of INV 600 mg TID as the sole PI is no longer recommended. Instead, INV is to be administered with RTV as the proposed BID combination regimen. FTV may be dosed as previously approved (1200 mg TID) or as recommended for approval in combination BID dosing with RTV.

XI. Appendix

A. Other Relevant Materials

1. Postmarketing safety data regarding co-administration of saquinavir and ritonavir

The applicant reviewed AEs in the Roche Drug Safety database (ADVENT) that were associated with the combined use of SQV (both formulations) and RTV (all SQV/RTV doses). All serious and non-serious cases received from spontaneous sources (e.g. health care professionals, regulatory authorities, literature reports, consumers) as well as all serious cases from clinical trials were recorded in the ADVENT database. Table 18 shows all AEs occurring at ≥ 1% of the 2592 reported events of all severities for SQV/RTV dosing combinations. Based on these data, the applicant notes that: 1) these AEs are frequently associated with SQV and/or RTV when either drug is administered by itself; 2) no AEs occurred with an unexpectedly high frequency; and 3) since these reactions are reported in a voluntary fashion from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to FTV exposure. From this Medical Officer's standpoint, these conclusions appear to be consistent with these data. Also, many of these AEs may also be associated with concomitant antiretroviral therapy (e.g. anemia with zidovudine administration, lactic acidosis associated with other antiretroviral agents).

Table 18. Number of AEs (Sorted by Descending Frequency) Reported with Saquinavir with Concomitant Ritonavir. Data Cumulative to November 30, 2002.

WHO SCO coding	Single AE cases			Pregnancy cases			Summary cases (N)	Total
	AE		CO	AE		CO		
	Serious	Non-Serious	N	Serious	Non-Serious	N		
Hypertriglyceridemia	49	34	3	8	-	-	-	94
Diarrhea	33	42	1	-	-	-	-	76
Nausea	20	31	11	2	-	-	-	64
Vomiting	33	16	13	-	-	-	-	62
Fever	33	9	19	-	-	-	-	61
Abdominal pain	16	14	21	-	1	1	-	53
Hypercholesterolemia	14	28	5	-	-	-	-	47
Anemia	28	4	4	7	1	-	-	44
Hepatic function abnormal	17	19	6	-	-	-	-	42
Pancreatitis	35	-	2	-	-	-	-	37
Lipodystrophy	11	21	1	-	-	-	1	34
Pneumonia	31	-	-	1	-	-	-	32
Drug interaction NOS	22	9	-	-	-	-	-	31
Lactic acidosis	17	1	1	10	1	-	-	30
Granulocytopenia	16	-	1	9	2	-	-	28
Myocardial infarction	27	-	-	-	-	-	-	27
Asthenia	13	4	9	-	-	-	-	26
Hyperlipemia	7	18	-	-	-	-	-	25

AE: adverse event; CO: comanifestations (signs and symptoms).
Source: NDA 20628 p. 1-196.

In response to the Division's request during the NDA review, the applicant provided nine periodic safety update reports for SQV up to 11/30/2002. These reports were reviewed

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-628 / S-020

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	DUE DATE 8/23/03	1. ORGANIZATION HFD-530	2. NDA NUMBER 20-628

3. NAME AND ADDRESS OF APPLICANT
Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199
Attn: A. Heather Knight-Trent, Pharm.D.

4. TYPE OF SUPPLEMENT
Labeling

5. DOCUMENT(S)

NUMBERS	DATED	RECEIVED
SE2-020	2/20/03	2/24/03

6. NAME OF DRUG
INVIRASE® Capsules

7. NONPROPRIETARY NAME
saquinavir mesylate capsules

8. SUPPLEMENT PROVIDES FOR:
Labeling changes to support the combination of saquinavir 1000 mg with ritonavir 100 mg BID

9. AMENDMENTS/DATES

10. PHARMACOLOGICAL CATEGORY
Anti-HIV

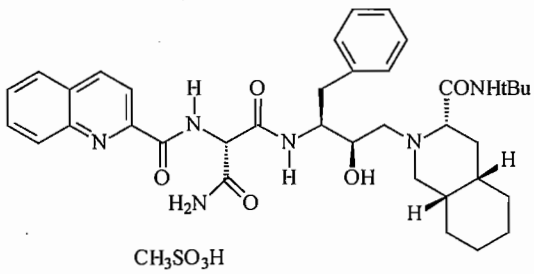
11. HOW DISPENSED
|X| Rx | | OTC

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM(S)
Hard gelatin capsules

14. POTENCY (CIES)
200 mg

15. CHEMICAL NAME AND STRUCTURE
[3S-[2[1R*(R*),2S*],3α,4aβ,8aβ]]-N[1]-[3-[[(1,1-dimethylethyl)amino]-carbonyl]octahydro-2-(1H)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)-propyl]-2-[(2-quinolinylcarbonyl)amino]butanediamide monomethanesulfonate salt



16. MEMORANDA

17. COMMENTS
This labeling supplement contains no CMC details and the dosage form and packaging are not affected. However, a categorical exclusion from the requirements to prepare an environmental assessment in accordance with 21 CFR 25.31(b) is claimed. Although the use of the active moiety is expected to increase it is not expected that the concentration in the aquatic environment will exceed [redacted] The concentration o[redacted] corresponds to approximately [redacted] of drug substance. In 2001 US sales of Invirase amounted to [redacted] capsules which corresponds to [redacted] of drug substance (Annual Report Y-006, dated 1/25/03). The proposed dose of 1000 mg BID (= 2000 mg/day) is only slightly larger than the current recommendation of 600 mg TID (=1800 mg/day).

18. CONCLUSIONS AND RECOMMENDATIONS
The request for a categorical exclusion from the requirements to prepare an environmental assessment is reasonable. There are no other CMC changes. This supplement is therefore recommended for approval from a CMC perspective.

19. REVIEWER

NAME	SIGNATURE	DATE OF DRAFT REVIEW
George Lunn, Ph.D.	*[signed electronically in DFS]*	3/19/03

20. CONCURRENCE: HFD-530/SMiller *[signed electronically in DFS]*

DFS CC LIST								
L = Action Letter	R	L	GLunn		L	Med: LLewis		PharmTox
R = Review	R	L	SMiller	R	L	PM: JO'Neill		Micro
	R	L	CChen			Biopharm		

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/s/

George Lunn
3/28/03 10:18:54 AM
CHEMIST

Invirase labeling supplement - EA question

Stephen Paul Miller
6/2/03 12:48:29 PM
CHEMIST

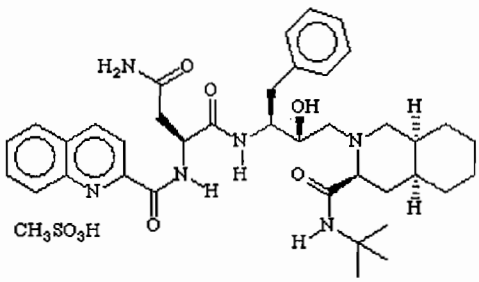
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-628 / S-020

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW COVER SHEET

NDA NUMBER:	**20-628 Supplemental**
NUMBER/DATE/TYPE:	020/2-20-2003/ SE2 NDA
INFORMATION TO SPONSOR	Yes (x) No ()
SPONSOR	Hoffmann-La Roche Inc., Nutley, New Jersey 07110
DRUG MANUFACTURER	Same as above
DIVISION NAME:	DAVDP
HFD #:	HFD-530
REVIEW COMPLETION	6/25/03
REVIEWER	Kuei-Meng Wu
DRUG TRADE NAME:	INVIRASE**Hard Gel Capsule,
GENERIC NAME	Saquinavir
CODE NAME	Ro 31-8959/003 (mesylate salt, CAS# 149845-06-7), Ro 31-8959/000 (free base, CAS# 127779-20-8)
CHEMICAL NAME	cis-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 methylsulfonate
FORMULA/MW	$C_{38}H_{50}N_6O_5.1:1CH_4O_3S$; MW: 767 (free base = 671)
STRUCTURE	
RELATED INDS	41,099, 43,861, 56,072
DRUG CLASS:	Antiviral
INDICATION:	Monotherapy and Combination Treatment (with HIVID and ZDV) for Patients with Advanced HIV Infections
CLINICAL FORMULATION:	Gelatine capsule 200 mg (as free base) (Inactive ingredients: lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc and magnesium stearate)
ROUTE	Oral
PROPOSED USE:	HIV Infection

DISCLAIMER: Tabular and graphical information is from sponsor's submission unless stated otherwise.

INTRODUCTION

Saquinavir (Ro 31-8959) is an antiviral drug developed as an oral therapy for the treatment of HIV infection. The antiviral activity of saquinavir results from inhibition of the HIV proteinase enzyme. This NDA drug product related to the hard gelatine capsule formulation of saquinavir (HGC) that has a very low oral bioavailability in both animals and man (~2.5%, ~4% and <12% in rat, man and marmoset, respectively). This low bioavailability results from a combination of poor, and saturable absorption (<20% in rat, ~30% in man), and rapid/saturable, metabolism of the drug.

REGULATORY COMMENTS

This supplemental NDA does not contain pharm/tox data, except an update of the drug's label that relates to addition of available carcinogenicity information on saquinavir. The carcinogenicity portion of the labeling is reviewed and slightly modified (2 places, bold and underlined) as below.

LABELING CHANGES

Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis:

Carcinogenicity studies found no indication of carcinogenic activity in rats and mice administered saquinavir for approximately 2 years. The plasma exposures (AUC values) in the respective species were up to 6-fold (rat) and 12-fold (mouse) higher than those obtained in humans at the recommended clinical dose.

KUEI-MENG WU, PH.D.
REVIEWING PHARMACOLOGIST
DAVDP

CONCURRENCES: HFD-530/ASSOC DIR/JFARREL

CC:
HFD-530 NDA 20-628(020)
HFD-530/DIVISION FILE

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/s/

Kuei Meng Wu
6/27/03 05:46:41 PM
PHARMACOLOGIST

James Farrelly
7/2/03 09:09:46 AM
PHARMACOLOGIST