Drug-Drug Interaction Study of Ketoconazole and Ritonavir-boosted Saquinavir

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Running title: Saquinavir, ritonavir, ketoconazole, protease inhibitor, HIV
Abstract

Saquinavir, a potent HIV protease inhibitor, is extensively metabolized by CYP3A4. Saquinavir is co-administered with ritonavir, a strong CYP3A4 inhibitor, to boost its exposure. Ketoconazole is a potent CYP3A inhibitor. The objectives of this study were to investigate the effect of ketoconazole on the pharmacokinetics of saquinavir/ritonavir and vice-versa using the approved dosage regimens of saquinavir/ritonavir 1000/100 mg twice daily and ketoconazole 200 mg once daily. This was an open-label, randomized two-arm, one-sequence, two-period crossover study in healthy subjects. In study arm 1, 20 subjects received saquinavir/ritonavir treatment alone for 14 days, followed in combination with ketoconazole treatment for 14 days. In arm 2, 12 subjects received ketoconazole treatment for 6 days, followed in combination with saquinavir/ritonavir treatment for 14 days. Pharmacokinetics were assessed on the last day of each treatment (days 14 and 28 in arm 1, and days 6 and 20 in arm 2). The exposures $C_{\text{max}}$ and $AUC_{0-12}$ of saquinavir and ritonavir with and without ketoconazole were not substantially altered after two weeks of concomitant dosing with ketoconazole. The $C_{\text{max}}$ and $AUC_{0-12}$ of ketoconazole, dosed 200 mg once daily, were increased by 45% (90% confidence interval: 32% to 59%) and 168% (90% confidence interval: 146% to 193%), respectively, after two weeks of concomitant dosing with ritonavir-boosted saquinavir (1000 mg saquinavir/100 mg ritonavir twice daily). The greater exposure to ketoconazole when given in combination with saquinavir/ritonavir was not associated with unacceptable safety or tolerability. No dose adjustment for saquinavir/ritonavir (1000/100 mg twice daily) is required when co-administered with 200 mg ketoconazole once daily and high doses of ketoconazole (> 200 mg/day) are not recommended.
Introduction

Saquinavir, a potent human immunodeficiency virus (HIV) protease inhibitor, is extensively metabolized by cytochrome P450 (CYP) 3A4 [1]. For the antiretroviral combination treatment of HIV-infected patients, saquinavir is co-administered with ritonavir, another HIV protease inhibitor and strong CYP 3A4 inhibitor [2], to boost the exposure of saquinavir. The new dosage form of saquinavir (Invirase®), a 500 mg film-coated tablet, was approved in 2004 in the USA and 2005 in Europe, and allows a lower pill burden using the dosing regimen of saquinavir/ritonavir 1000/100 mg twice daily which was approved in 2003. Saquinavir exhibits a pronounced food effect, and patients are advised to take saquinavir with ritonavir always with a full meal [1]. The imidazole antifungal compound ketoconazole is effective in the treatment of oropharyngeal candidiasis being the most common infection among persons infected with HIV [3]. Ketoconazole is also known as a prototypic and strong CYP3A inhibitor [4], and is a recommended drug of choice to investigate the interaction with CYP3A4 substrates like saquinavir [6]. It has already been shown that co-administration of ketoconazole 200 mg or 400 mg once daily with saquinavir/ritonavir 400/400 mg twice daily resulted in increased area under the drug plasma concentration-time curve (AUC) and peak plasma concentrations (C\text{max}) for saquinavir and ritonavir, whereas the effect of saquinavir/ritonavir on the pharmacokinetics of ketoconazole was not evaluated [5]. The present study was performed using the approved dosing regimens of saquinavir/ritonavir 1000/100 mg twice daily and ketoconazole 200 mg once daily, and documents the drug-drug interaction after two weeks of concomitant dosing in both directions, i.e. the effect of ketoconazole on the pharmacokinetics of saquinavir/ritonavir and that of
saquinavir/ritonavir on ketoconazole. The objective of the study was to provide appropriate dosing guidelines to clinicians who treat HIV patients with saquinavir/ritonavir and ketoconazole.

Materials and Methods

Study design and population. This was an open-label, randomized two-arm, one-sequence, two-period crossover study conducted in healthy male and female subjects. Subjects had to give written informed consent, and the study protocol was approved by the IRB Institutional Review Board (Comité Consultatif de Protections des Personnes dans la Recherche Biomédicale, Strasbourg, France). The study was conducted in full compliance with the principles of the “Declaration of Helsinki III” and performed according to the guidelines of Good Clinical Practice.

In order to enable stable pharmacokinetic conditions for saquinavir/ritonavir, the combination of these two drugs was administered for two weeks, ketoconazole alone was dosed for six days, and the combination of ritonavir/saquinavir with ketoconazole was administered in both study arms for another two weeks. In study arm 1, saquinavir/ritonavir was administered first (period 1), followed by the addition of ketoconazole (period 2), and in study arm 2, ketoconazole was dosed first (period 1), followed by the addition of saquinavir/ritonavir (period 2). The planned sample size for study arm 1 was N=20 assuming a within-subject coefficient of variation (CV) of up to 30% for saquinavir AUC and C\text{max}, which was based on the observed within-subject CV of 27% and 24% for these parameters, respectively, from a previous study (BP17359,
Roche data on file). For study arm 2, the sample size was set to N=12 assuming a within-subject CV of up to 16% for ketoconazole AUC and C\text{max} based on the respective values of 16% and 14% observed in a previous study (WK14435, Roche data on file). These sample sizes would ensure that, with a probability of at least 80%, the two-sided 90% confidence interval for the geometric population mean of the individual parameter ratios (period 2/period 1) would be for saquinavir within 75% to 133% of the geometric population mean, and for ketoconazole within 80% to 125% of the geometric population mean. Subjects were randomized to study arms 1 and 2 with a block size of 8 (5 to arm 1, 3 to arm 2).

Subjects underwent screening evaluations to determine eligibility within 28 days prior to study enrollment. Screening procedures included amongst others testings for HIV, hepatitis B and C, and testing for pregnancy in women. Healthy male and female subjects, aged 18 -65 years (inclusive) with body mass index between 18 to 30 kg/m\textsuperscript{2} and being non-smokers, were enrolled into the study. Intake of grapefruit or grapefruit juice was not allowed from two weeks prior to the first dose and during the study. In addition, consumption of alcohol was not permitted during the study. Subjects were instructed to take the study drugs always with a meal. No concomitant medications were permitted during the study with the exception to treat adverse events. Subjects who were on concomitant treatment with drugs known as CYP3A4 substrates, CYP3A4 inhibitors, or CYP3A4 inducers were excluded from the study. Women in the study had to be of non-child-bearing potential or under efficient non-hormonal contraception throughout the study and until at least one month thereafter.
In study arm 1, saquinavir/ritonavir 1000/100 mg was dosed twice daily for 28 days (excluding the evening dose on day 14), with ketoconazole 200 mg once daily added from day 15 to 28 (period 1: day 1 to 14; period 2: day 15 to 28). In study arm 2, ketoconazole 200 mg was dosed once daily for 20 days with saquinavir/ritonavir 1000/100 mg twice daily added from day 7 to 20 (period 1: day 1 to 6; period 2: day 7 to 20). In study arm 1, pharmacokinetics were assessed for saquinavir/ritonavir over 12 hours on days 14 and 28, and in arm 2 for ketoconazole over 24 hours on days 6 and 20. Study drugs were administered 30 minutes after the start of a standard high fat, high calorie (63g fat, 975 kcal) breakfast on days 14 and 28 for arm 1, or days 6 and 20 for arm 2. Plasma samples for pharmacokinetic assessments were collected at pre-dose, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours post-dose (13 samples). In study arm 1, subjects received on days 14 and 28 saquinavir and ritonavir doses only in the morning. In arm 1, plasma samples were analyzed for saquinavir and ritonavir, and in arm 2 for ketoconazole. In both study arms additional pre-dose concentration measurements were made on the last 2 to 4 days of periods 1 and 2 to document stable pharmacokinetic conditions. In study arms 1 and 2, during both pharmacokinetic assessment periods, subjects were confined to the study center. Safety parameters included medical history, physical examination, standard safety laboratory assessments (hematology, blood chemistry, urinalysis), vital signs and serial ECGs recorded at pre-specified time points throughout the trial, as well as urine drugs of abuse-, alcohol breath tests, and urine pregnancy tests (in females only). A medical follow-up examination was conducted 15 to 21 days after the last dose of study drugs. All subjects were observed for adverse events during the entire study period.
Bioanalysis. For the determination of saquinavir and ritonavir pharmacokinetics, blood samples of 5.5 mLs were collected by peripheral venous catheter or venipuncture into tubes containing lithium heparin as the anticoagulant, and for pharmacokinetics of ketoconazole, blood samples of 2.6 mLs were collected into EDTA containing tubes. Plasma was separated by centrifugation for 10 minutes at 1500 g and 4°C. Total plasma concentrations of saquinavir and ritonavir were analyzed by PRA International – Early Development Services (formerly called Pharma Bio-Research Group B.V, Assen, The Netherlands) using a validated HPLC-MS/MS method (high performance liquid chromatography coupled with tandem mass spectrometry) with two linear concentration ranges. The low calibration range was 1.00 ng/mL to 100 ng/mL for both analytes, using aliquots of 200 µL plasma. The high calibration range was 10-10,000 ng/mL for both analytes, using aliquots of 100 µL plasma. The precision of the low concentration assay ranged from 0.7 to 7.0% for saquinavir, and from 3.6 to 7.8% for ritonavir. The accuracy ranged from 93.1 to 100.2% and from 94.2 to 95.8% for saquinavir and ritonavir, respectively. The precision of the high concentration assay ranged from 3.5 to 6.8% for saquinavir, and from 4.2 to 6.1% for ritonavir. The accuracy ranged from 98.9 to 101.4% and from 95.0 to 103.5% for saquinavir and ritonavir, respectively. Total ketoconazole plasma concentrations were analyzed by AAI Pharma Deutschland GmbH & Co. KG (formerly called AAI Deutschland GmbH & Co. KG, Neu-Ulm, Germany) using a validated HPLC-fluorescence method with a calibration range from 25.0 to 2500 ng/mL, using aliquots of 100 µL plasma. The precision ranged from 2.2 to 6.0% and the accuracy from 97.8 to 101.0%.
Pharmacokinetic Evaluation. Pharmacokinetic parameters were estimated using standard non-compartmental methods (Software WinNonlin Professional, Version 5.2, Pharsight Corporation, Mountainview, CA) and actual sampling times. The following pharmacokinetic parameters were directly obtained from the observed concentration-versus-time data: the maximum plasma concentration (C_{max}), the time to C_{max} (T_{max}), the drug concentration at 12 hours after administration (C_{12}) for saquinavir/ritonavir, or at 24 hours after administration (C_{24}) for ketoconazole. The area under the drug plasma concentration-time curve from time zero until 12 hours (AUC_{0-12}) for saquinavir/ritonavir, or until 24 hours (AUC_{0-24}) for ketoconazole, was calculated applying the linear trapezoidal rule. The terminal elimination half-life (t_{1/2}) was estimated by ln2/k_{el} where k_{el} is the terminal elimination rate constant determined by linear regression of the last 4 natural-log transformed concentration time points with maximum excluding 1 intermediate concentration time point and fitting with an adjusted residuals squared value of being equal to or greater than 0.90. The apparent oral plasma clearance at steady-state (CL/F) was estimated by Dose/AUC_{0-12} for saquinavir and ritonavir, and by Dose/AUC_{0-24} for ketoconazole.

Statistical Analysis. In both study arms, predose concentrations measured on the last 2 to 4 days of periods 1 and 2 were summarized per study arm and study day. Pharmacokinetic parameters were summarized per study arm and treatment for all subjects who have completed the trial. For the assessment of the drug-drug interaction, the study variables were AUC_{0-12} and C_{max} for saquinavir/ritonavir, and AUC_{0-24} and C_{max} for ketoconazole. Natural log-transformed values of these parameters were used, and the
exposure ratios determined in arm 1 for saquinavir and ritonavir of day 28 to day 14, and in arm 2 for ketoconazole of day 20 to day 6. The geometric means of the individual exposure ratios, together with the corresponding two-sided 90% confidence intervals (CIs), were calculated. No formal confirmatory hypothesis testing was planned and p-values were to be interpreted in an exploratory manner. The statistical analysis was performed using software SAS V8.2 (SAS Institute Inc, Cary, NC, USA).

Results

Demographics. A total of 42 healthy subjects were enrolled in this study. Twenty-nine subjects (27 males / 2 females) were randomly assigned to study arm 1 assessing the effect of ketoconazole on the plasma concentrations of saquinavir/ritonavir, and 13 subjects (all males) were randomly assigned to study arm 2 assessing the effect of saquinavir/ritonavir and the plasma concentrations of ketoconazole. Each of the 42 subjects received at least 1 dose of study drug(s) and 32 subjects (20 in arm 1, 12 in arm 2) completed the study as planned. The demographic characteristics of the study population are shown in Table 1.

Evaluation of predose concentrations. Serial predose measurements of the last 2 to 4 days of each treatment period are summarized per study arm and treatment day in Tables 2 and 3. In study arm 1, the daily saquinavir and ritonavir predose concentrations were of similar magnitude within each measured period, with pronounced but comparable
interindividual variabilities expressed as CV% in both periods (Table 2). In addition, the daily saquinavir and ritonavir predose concentrations were of similar dimension in the absence and presence of ketoconazole co-administration. Likewise, in arm 2, the daily ketoconazole predose concentrations were stable within each measured period, but were approximately 17-fold higher in presence of saquinavir/ritonavir co-administration as compared to ketoconazole treatment alone (Table 3). Also, in study arm 2 period 2, the daily saquinavir and ritonavir predose concentrations were not dissimilar from those seen for saquinavir/ritonavir throughout study arm 1.

Assessment of the drug-drug interactions. The pharmacokinetic interaction was evaluated in the 20 subjects in arm 1 and the 12 subjects in arm 2, who completed the entire study. Figures 1 shows the 12 hour plasma log-transformed concentration versus time profiles of saquinavir/ritonavir in the absence (day 14) and presence of ketoconazole co-administration (day 28) in study arm 1, Figure 2 shows the respective 24 hour profiles of ketoconazole in the absence (day 6) and presence of saquinavir/ritonavir co-administration (day 20) in study arm 2. Summaries of the pharmacokinetic parameters for saquinavir/ritonavir (study arm 1) with or without ketoconazole co-administration are presented in Table 4, and those for ketoconazole with or without saquinavir/ritonavir co-administration in Table 5.

In study arm 1, differences in the plasma concentration versus time profiles for saquinavir and ritonavir during co-administration with and without ketoconazole were small and not clinically meaningful. Mean values for all pharmacokinetic parameters of saquinavir and ritonavir were similar in the absence and presence of ketoconazole co-administration, and
the inter-individual variability (as expressed by CV%) was similar for both compounds and in both of the two treatment periods. The geometric mean ratio estimates for AUC$_{0-12}$ and C$_{max}$ of saquinavir and ritonavir were close to 1, and all four 90% CIs were within the range of 0.86 to 1.26 (Tables 4 and 5). Based on these results, it can be concluded that the addition of ketoconazole at a dose of 200 mg once daily to the approved therapeutic regimen of saquinavir/ritonavir 1000/100 mg twice daily for 14 days did not have a clinically relevant effect on the pharmacokinetic exposures of saquinavir or ritonavir.

In study arm 2, the plasma concentration versus time profiles showed a considerable increase in ketoconazole exposure during co-administration with saquinavir/ritonavir. The terminal elimination of ketoconazole was prolonged following 14 days of co-administration with saquinavir/ritonavir, as indicated by the flatter decline in the log-transformed concentration versus time profile. The absorption of ketoconazole was minimally prolonged during saquinavir/ritonavir co-administration as expressed by a 1-hour delay in the median T$_{max}$, from 2.5 hours in period 1 to 3.5 hours in period 2. The median t$_{ss}$ was also prolonged from 4.3 hours in period 1 to 10.7 hours in period 2, and the geometric mean CL$_{ss}$/F value was decreased by more than 50% with saquinavir/ritonavir co-administration, from 8.22 to 3.07 L/hour. Increases in the mean C$_{24}$ values for ketoconazole of > 10-fold were seen in period 2 relative to period 1. The intersubject variabilities (as expressed by CV%) were comparable in periods 1 and 2 for ketoconazole. The geometric mean ratio estimates for AUC$_{0-24}$ and C$_{max}$ of ketoconazole were substantially larger than 1 (Table 5). Following 14 days of co-administration of
saquinavir/ritonavir, the mean ketoconazole AUC$_{0-24}$ and $C_{\text{max}}$ were increased by 2.68- and 1.45-fold, respectively, compared with administration of ketoconazole alone.

**Safety Results.** The study medications were generally well tolerated by healthy subjects. There were ten early discontinuations from the study: 9 in arm 1, and 1 in study arm 2. Reasons for study withdrawals were adverse events in 6 subjects in arm 1, elevated safety laboratory parameters (high triglycerides and LDL cholesterol, respectively) in 2 subjects in arm 1, and other reasons in the remaining 1 subject in arm 1 and the 1 subject in arm 2. In study arm 1, the adverse events reporting rates were similar in period 1 (days 1 to 14) and period 2 (days 15 to 28), with 62% and 58% of subjects, respectively. Gastrointestinal disorders were the most frequently adverse events reported by 41% and 25% of subjects in period 1 and period 2, respectively, followed by events related to infections and infestations, and nervous system disorders reported by 17% of subjects each during saquinavir/ritonavir treatment in period 1. In study arm 2, the reporting rate for adverse events was lower during period 1 (days 1 to 6) with 23% of subjects as compared with that of 92% of subjects in period 2 (days 7 to 20). Again, gastrointestinal disorders were the most prominent adverse events reported by 54% during triple combination therapy in period 2. The majority of the adverse events were mild to moderate in intensity. All adverse events were resolved without sequelae. The greater exposure to ketoconazole when given in combination with saquinavir/ritonavir was not associated with unacceptable safety or tolerability in this study.
Discussion

In order to assess the impact of drug-drug interaction at the CYP3A4 metabolic pathway, strict exclusion criteria were set in this study with regard to concomitant use of CYP3A4 substrates, -inhibitors, or -inducers. As hormonal contraceptives, being CYP3A4 substrates, were not allowed, women had to be of non-child-bearing potential or under efficient non-hormonal contraceptive protection. With these requirements, only two women could be recruited into this study. Both were randomized to study arm 1 and completed all study procedures. Knowing that for saquinavir statistically significant greater exposures have been observed in women than in men (study BP17359 with 87 males and 7 females; Roche data on file), the exposures of the two women to saquinavir (AUC$_{0-12}$ 47.7 and 43.4 µg·hr/mL in period 1, and 29.8 and 66.0 µg·hr/mL in period 2) in this study in both periods were similar to those seen in the remaining 18 men within 40 to 53% variability (Table 4), and therefore the conclusions made for the whole population in this study arm may also apply to female patients. On the other hand, the effect of saquinavir and ritonavir on the exposure of ketoconazole (arm 2) was only studied in men. However, lacking data of female subjects in this study arm, and considering also the related safety aspects, it cannot be assumed that this increase in ketoconazole exposure during concomitant saquinavir/ritonavir 1000/100 twice daily treatment would be of different magnitude in women.

In this study in healthy volunteers, the addition of ketoconazole at a dose of 200 mg once daily to the approved therapeutic dosing regimen of saquinavir/ritonavir 1000/100 mg twice daily for 2 weeks did not have a clinically relevant effect on the pharmacokinetic exposures of saquinavir and ritonavir. For both compounds, the 90% CIs surrounding the
geometric mean ratio estimates for AUC\(_{0-12}\) and \(C_{\text{max}}\) were within, or only 1% exceeding the upper limit of the no effect boundary (0.80 to 1.25) as defined in the FDA guidance for industry for in vivo drug interaction studies [6].

By comparison, following 6 days of pretreatment with ketoconazole 200 mg once daily, the addition of saquinavir/ritonavir 1000/100 mg twice daily for 2 weeks increased the exposure of ketoconazole by 2.68 (2.46-2.93)-fold for AUC\(_{0-24}\) and by 1.45 (1.32-1.59)-fold for \(C_{\text{max}}\). The median elimination half-life for ketoconazole was also more than doubled, from 4.3 hours following treatment with ketoconazole alone, to 10.7 hours following co-administration with saquinavir/ritonavir. The reduced clearance of ketoconazole resulted in predose concentrations of ketoconazole that were more than 10-fold higher in all subjects following co-administration with saquinavir/ritonavir compared with values seen after 6 days of treatment with ketoconazole alone.

The two week treatment phases of 1) saquinavir/ritonavir and 2) the concomitant triple drug treatment with ketoconazole was considered sufficient in order to achieve stable pharmacokinetic conditions for all three medications involved. This treatment duration, although longer than required based on the half-lives of ritonavir and saquinavir, was selected based on the fact that ritonavir not only inhibits the metabolism of CYP 3A4, but also increases the enzyme activity of CYP 3A4 (inhibition associated induction). Due to this auto-induction, plasma concentrations of saquinavir/ritonavir generally reach steady-state two weeks after the start of ritonavir administration [7].

Studies have already been performed investigating the drug-drug interaction between ketoconazole and saquinavir, or ritonavir, or saquinavir/ritonavir employing several dosing regimens. In these studies, the saquinavir and ritonavir doses used were different
from the approved dosing regimen for saquinavir/ritonavir 1000/100 mg twice daily. Coadministration of ketoconazole 400 mg once daily with saquinavir 1200 mg three times daily increased the AUC of saquinavir by 190%, but saquinavir did not change the AUC of ketoconazole [1]. Coadministration of ritonavir 500 mg twice daily with ketoconazole 200 mg once daily resulted in a 3.4-fold increase in ketoconazole AUC and an 18% increase in ritonavir AUC [2]. Coadministration of saquinavir/ritonavir 400/400 mg twice daily with ketoconazole 200 or 400 mg once daily showed an increase in saquinavir AUC by 37% and ritonavir AUC by 29% [5]. The results of the present study are closest to those obtained with the ritonavir and ketoconazole combination [2], although the increase in ketoconazole exposure was somewhat less for AUC in the present study (2.68-fold versus 3.4-fold in reference [2]) and C\text{\textsubscript{max}} (45% in present study versus 55% in reference [2]). The metabolism and elimination of ketoconazole are clearly affected by the CYP3A4 inhibitory effect of ritonavir, whereas the influence of ketoconazole, a CYP3A- and P-gp inhibitor on the saquinavir/ritonavir combination is small as shown by the clinically irrelevant increases in plasma exposures of these two compounds. In the present study, the CYP3A4 inhibitory effect of ketoconazole on saquinavir, as seen in the above saquinavir ketoconazole interaction studies, is, for the most extent, superimposed by the CYP3A4 inhibitory effect of ritonavir on saquinavir. The increase in saquinavir AUC by 37% and ritonavir AUC by 29% when combined with ketoconazole, as observed in an earlier study [5], may have been due to the higher ketoconazole dose (400 mg) and/or different saquinavir/ritonavir doses (400/400 mg) used compared with the present study. A full CYP3A inhibitory effect of ketoconazole may not have been reached with the ketoconazole standard dose of 200 mg daily in the present study. However, based on the existing data, and for safety reasons, a
ketoconazole multiple dose regimen of 400 mg daily was not considered acceptable for this study in healthy volunteers knowing of the hepatic toxicity liability of ketoconazole [9], and respecting the maximum 200 mg daily ketoconazole dose recommendations in combination with ritonavir [2]. With a ketoconazole 400 mg daily dose in the present study, further increases of ketoconazole plasma concentrations would have been most likely.

The safety results as recorded by adverse events and laboratory safety measurements were consistent with those indicated in the respective product information for these three drugs [1, 2, 8]. There were no vital sign or ECG abnormalities of clinical relevance recorded during this study.

**Conclusions**

The present two-arm drug-drug interaction study involving 200 mg/day ketoconazole and ritonavir-boosted saquinavir (1000 mg saquinavir/100 mg ritonavir twice daily) indicated that $C_{\text{max}}$ and $AUC_{0-12}$ of both saquinavir and ritonavir are not substantially altered by the addition of ketoconazole for the duration of two weeks, but that, on the other hand, $C_{\text{max}}$ and $AUC_{0-24}$ of ketoconazole are increased by 45% and 168%, respectively, after the addition of saquinavir/ritonavir for two weeks. The greater exposure to ketoconazole when given in combination with saquinavir/ritonavir was not associated with unacceptable safety or tolerability. It is concluded that no dose adjustment for either saquinavir or ritonavir is required when co-administered with $\leq 200$ mg ketoconazole.
once daily and, based on the hepatotoxicity liability of ketoconazole, high doses of ketoconazole (> 200 mg/day) are not recommended.

Acknowledgement

We thank the study team members at Hoffman-La Roche for their assistance with the study. All authors are Roche employees.
References


2. **Abbott Laboratories.** 2006. Product information for Norvir® 100 mg capsule.


### TABLE 1. Summary of Demographic characteristics of the study populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study arm 1 (N = 29)</th>
<th>Study arm 2 (N = 13)</th>
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<tr>
<td>Male/ Female</td>
<td>27/2</td>
<td>13/0</td>
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<tr>
<td>Black/Caucasian</td>
<td>1/28</td>
<td>0/13</td>
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<tr>
<td>Mean age (range), years</td>
<td>33.0 (19 – 62)</td>
<td>30.5 (19 – 58)</td>
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<tr>
<td>Mean body weight (range), kg</td>
<td>76.7 (45.0 – 107.8)</td>
<td>80.4 (64.7 – 100.0)</td>
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<td>Mean body mass index (range), kg/m²</td>
<td>24.5 (18.0 – 29.5)</td>
<td>25.1 (20.1 – 29.2)</td>
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TABLE 2: Geometric mean (CV%) of predose plasma concentrations of saquinavir/ritonavir in study arm 1 (N ≤ 29)

<table>
<thead>
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<tr>
<td></td>
<td>11</td>
<td>12</td>
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<tr>
<td>Saquinavir, µg/mL</td>
<td>0.84 (120)</td>
<td>0.97 (71)</td>
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<tr>
<td>Ritonavir, µg/mL</td>
<td>0.29 (130)</td>
<td>0.33 (76)</td>
</tr>
<tr>
<td>Ketoconazole, µg/mL</td>
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<tr>
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<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
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<td>Saquinavir, µg/mL</td>
<td>0.99 (74)</td>
<td>1.3 (84)</td>
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<td>0.84 (120)</td>
<td>1.0 (100)</td>
<td>1.3 (66)</td>
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<td>Ritonavir, µg/mL</td>
<td>0.38 (40)</td>
<td>0.38 (74)</td>
<td>0.32 (89)</td>
<td>0.30 (84)</td>
<td>0.40 (75)</td>
<td>0.45 (59)</td>
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<tr>
<td>Ketoconazole, µg/mL</td>
<td>-</td>
<td>-</td>
<td>0.93 (44)</td>
<td>1.0 (38)</td>
<td>1.0 (44)</td>
<td>1.1 (36)</td>
</tr>
</tbody>
</table>

CV%: coefficient of variation

TABLE 3: Geometric mean (CV%) of predose plasma concentrations of ketoconazole and saquinavir/ritonavir in study arm 2 (N ≤ 13)

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<tr>
<td>Ketoconazole, µg/mL</td>
<td>0.072 (51)</td>
<td>0.070 (60)</td>
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<tr>
<td>Saquinavir, µg/mL</td>
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<td>-</td>
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<tr>
<td>Ritonavir, µg/mL</td>
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<th>18</th>
<th>19</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole, µg/mL</td>
<td>1.2 (54)</td>
<td>1.3 (54)</td>
<td>1.2 (47)</td>
<td>1.2 (61)</td>
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<tr>
<td>Saquinavir, µg/mL</td>
<td>1.1 (42)</td>
<td>1.1 (57)</td>
<td>0.83 (62)</td>
<td>1.3 (72)</td>
</tr>
<tr>
<td>Ritonavir, µg/mL</td>
<td>0.48 (36)</td>
<td>0.40 (45)</td>
<td>0.42 (70)</td>
<td>0.51 (57)</td>
</tr>
</tbody>
</table>

CV%: coefficient of variation
### TABLE 4: Summary of pharmacokinetic parameters for saquinavir and ritonavir in study arm 1 (N=20)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Geometric mean ratio (90% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Geometric mean ratio (90% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ ritonavir</td>
<td>+ ritonavir + ketoconazole</td>
<td>Geometric mean ratio</td>
<td>+ saquinavir</td>
<td>+ saquinavir + ketoconazole</td>
<td>Geometric mean ratio</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;, µg/mL</strong></td>
<td>5.01 (51.5)</td>
<td>5.10 (36.3)</td>
<td>1.02 (0.86-1.20)</td>
<td>1.53 (39.4)</td>
<td>1.66 (26.4)</td>
<td>1.08 (0.96-1.21)</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-12&lt;/sub&gt;, µg⋅hr/mL</strong></td>
<td>30.0 (53.3)</td>
<td>32.2 (40.3)</td>
<td>1.07 (0.92-1.26)</td>
<td>8.9 (36.3)</td>
<td>9.95 (30.3)</td>
<td>1.12 (1.03-1.22)</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;12&lt;/sub&gt;, µg/mL</strong></td>
<td>0.956 (56.3)</td>
<td>1.13 (62.4)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.230 (57.1)</td>
<td>0.292 (57.7)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt;, hour</strong></td>
<td>3.0 (2.0 – 6.0)</td>
<td>3.0 (2.0 – 5.0)</td>
<td>NA</td>
<td>4.0 (2.0 – 5.0)</td>
<td>4.0 (1.0 – 5.0)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>t&lt;sub&gt;1/2&lt;/sub&gt;, hour</strong></td>
<td>4.9 (4.1 – 5.9)</td>
<td>5.2 (4.5 – 6.8)</td>
<td>NA</td>
<td>3.7 (3.1 – 5.6)</td>
<td>4.2 (3.5 – 5.5)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>CL&lt;sub&gt;ss&lt;/sub&gt;/F, L/hour</strong></td>
<td>33.4 (53.3)</td>
<td>25.6 (43.3)</td>
<td>NA</td>
<td>11.2 (36.3)</td>
<td>11.7 (32.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>C<sub>max</sub>, maximum plasma concentration; AUC<sub>0-12</sub>, area under the drug plasma concentration-time curve from time zero to 12 hours; C<sub>12</sub>, plasma concentration at 12 hours; T<sub>max</sub>, time to C<sub>max</sub>; t<sub>1/2</sub>, terminal elimination half-life; CL<sub>ss</sub>/F, apparent oral clearance at steady state.

<sup>b</sup>Ratio of period 2/period 1.

<sup>c</sup>NA, not assessed.
TABLE 5: Summary of pharmacokinetic parameters for ketoconazole in study arm 2 (N=12)

<table>
<thead>
<tr>
<th>Parameter&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Geometric mean ratio (90% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketoconazole alone [geometric mean (CV%)]</td>
<td>+ saquinavir + ritonavir [geometric mean (CV%)]</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, µg/mL</td>
<td>3.86 (28.9)</td>
<td>5.59 (29.1)</td>
<td>1.45 (1.32-1.59)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;, µg⋅hr/mL</td>
<td>24.3 (36.4)</td>
<td>65.2 (32.1)</td>
<td>2.68 (2.46-2.93)</td>
</tr>
<tr>
<td>C&lt;sub&gt;24&lt;/sub&gt;, ng/mL</td>
<td>87.4 (79.7)</td>
<td>1.100 (47.8)</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;, hour</td>
<td>2.5 (2.0 – 5.0)</td>
<td>3.5 (2.0 – 4.0)</td>
<td>NA</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;, hour</td>
<td>4.3 (2.1 – 7.0)</td>
<td>10.7 (6.7 – 18.5)</td>
<td>NA</td>
</tr>
<tr>
<td>CL&lt;sub&gt;ss&lt;/sub&gt;/F, L/hour</td>
<td>8.22 (36.4)</td>
<td>3.07 (32.1)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>C<sub>max</sub>, maximum plasma concentration; AUC<sub>0-24</sub>, area under the drug plasma concentration-time curve from time zero to 24 hours; C<sub>24</sub>, plasma concentration at 24 hours; T<sub>max</sub>, time to C<sub>max</sub>; t<sub>1/2</sub>, terminal elimination half-life; CL<sub>ss</sub>/F, apparent oral plasma clearance at steady-state.

<sup>b</sup>Ratio of period 2 / period 1.

<sup>c</sup>NA, not assessed.
FIG 1. Mean plasma concentration-time profiles of saquinavir (squares) and ritonavir (circles) after 14 days of saquinavir/ritonavir 1000/100 mg twice daily administration (open symbols, dotted line), and after 14 days of co-administration of saquinavir/ritonavir with ketoconazole 200 mg once daily (filled symbols, solid line). SD is shown as error bar.
FIG 2. Mean plasma concentration-time profiles of ketoconazole after 6 days of ketoconazole 200 mg once daily administration (open symbols, dotted line) and after 14 days of co-administration of ketoconazole with saquinavir/ritonavir 1000/100 mg twice daily (filled symbols, solid line). SD is shown as error bar.