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SAQUINAVIR 500 MG TABLET, A NEW FORMULATION, HAS SIMILAR BIOAVAILABILITY TO INVIRASE 200 MG CAPSULE FOR HEALTHY VOLUNTEERS AT 1000/100 MG *BID* DOSING WITH RITONAVIR

Y. Hijazi[1], M. Riek[1], E. Gaudeul-Ehrhart[2] and S. Grange[1]
[1]Roche, Basel, Switzerland; [2]Clinical Pharmacology Unit of Roche, Strasbourg, France
Youssef.hijazi@roche.com

Background

Saquinavir (SQV), an HIV protease inhibitor, is widely used for the treatment of HIV infection. Two 200 mg formulations are currently marketed for oral administration: Invirase, a hard gelatin capsule (saquinavir mesylate); and Fortovase, a soft gelatin capsule (saquinavir base). These formulations have shown good efficacy and safety when boosted with ritonavir (r) at a SQV/r dosage regimen of 1000/100 mg *bid*.[1–4] Saquinavir is approved in the EU for administration as SQV/r, 1000/100 mg *bid*, as either the Invirase or Fortovase formulations.

Ritonavir enhances the oral bioavailability of SQV by inhibiting CYP3A4- and P-gp-mediated metabolism and transport of SQV.[5–7] Ritonavir also increases the activity of CYP3A4 through an inhibition-associated induction mechanism that requires repeated administration of ritonavir for 1–2 weeks to obtain a stable effect on CYP3A4 activity.[8]

The pill count for a SQV/r regimen (1000/100 mg *bid*), using the current 200 mg formulation, is 12 pills per day (5 SQV capsules + 1 ritonavir capsule, *bid*). Roche is developing a 500 mg saquinavir mesylate tablet, using aqueous granulation technology and standard excipients, that is smaller than the existing 200 mg formulation **(Figure 1)** and will allow the use of only two SQV tablets twice daily in combination with ritonavir. The lower pill count and improved convenience may improve adherence to SQV/r regimens.

A study was conducted in healthy volunteers to determine the bioavailability of the new SQV 500 mg tablet formulation (SQVtablet) relative to Invirase capsules, when both are taken with ritonavir.

Figure 1. Relative sizes of the new saquinavir 500 mg tablet and the Invirase and Fortovase formulations (saquinavir 200 mg)

Study Objective

To determine the bioavailability of the 500 mg tablet formulation of saquinavir mesylate relative to the Invirase 200 mg capsule, following single dose administration of 1000 mg with 100 mg ritonavir *bid* after a high fat breakfast.

Methods

1. Subjects

Twenty healthy, male, non-smoking volunteers of mean age 30 years (range: 19–56 years) and mean body mass index of 24 kg/m² (range: 19–29 kg/m²).

2. Study design

Open-label, randomised, four-period, two-treatment, two-sequence replicated crossover, with a washout period of 2 days. All subjects received ritonavir (100 mg *bid*) from days 1–24. On the mornings of days 14, 17, 20 and 23, subjects were randomised to receive:

(A) 5 x 200 mg Invirase capsules + 1 x 100 mg ritonavir capsule; or

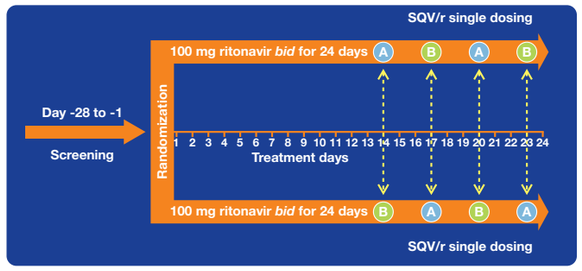
(B) 2 x 500 mg saquinavir mesylate tablets + 1 x 100 mg ritonavir capsule

In either sequence **ABAB** or **BABA (Figure 2)**, after an overnight fast, subjects took saquinavir and ritonavir with 180 ml of water within 30 minutes of receiving a standard high-fat breakfast (800–1000 Calories, 50% from fat). Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, and 24 hours after the administration of SQV.

3. Drug assay

Plasma saquinavir concentrations were determined by a validated HPLC-MS/MS method developed at Roche. The limit of quantification of the assay was 0.2 ng/ml, the precision was represented by a CV < 4.5%, and the inaccuracy was below 1.9%.

Figure 2. Study design



4. Pharmacokinetic and statistical analysis

Pharmacokinetic parameters were estimated using WinNonlin 4.0.1 (Pharsight Corporation, Mountain View, CA, USA) and standard non-compartmental methods. The parameters AUC_{0-last}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$ and CL/F were determined. The apparent elimination rate constant (k) was estimated by linear regression of the logarithm of the plasma concentration versus time data, from the terminal phase using at least three concentration-time points. The apparent elimination half-life ($t_{1/2}$) was calculated from ln(2)/k.

The area under the concentration-time curve from zero to infinity ($AUC_{0-\infty}$) was extrapolated by adding the ratio of C_{last}/k to AUC_{0-last}, where AUC_{0-last} is the area under the concentration-time curve from zero to C_{last} calculated using the linear trapezoidal rule and C_{last} is the last measurable concentration. The oral clearance CL/F after a single dose was calculated by dose/$AUC_{0-\infty}$. The C_{max} was determined as the highest observed concentration, and T_{max} is the time corresponding to this concentration.

Relative bioavailability was assessed as the mean exposure ratio of SQV_{tablet} relative to Invirase, based on $AUC_{0-\infty}$ and C_{max}. The estimated relative bioavailability and its 90% confidence interval (CI) were calculated using the corresponding contrast from an ANOVA with four factors (sequence, period, treatment, and subject [random effect]) on log transformed $AUC_{0-\infty}$ and C_{max} (FDA guidance for industry on standard approaches to establishing bioequivalence, January 2001).

Results

1. Study conduct and subject disposition

Four subjects discontinued at different time points. One due to a gastrointestinal adverse event prior to the first saquinavir administration, the others for either protocol violation or withdrawal of consent.

Occasional deviations in breakfast content from the protocol-defined standard were noted (< 10% difference in caloric content; ≤ 16% difference in fat content). Affected data were excluded for the evaluation of relative bioavailability, but were considered for the pharmacokinetic analyses.

2. Pharmacokinetic results

- Pharmacokinetic profiles of saquinavir after Invirase/r and SQV_{tablet}/r are shown in **Figure 3.**
- Pharmacokinetic parameters of saquinavir after Invirase/r and SQV_{tablet}/r are presented in **Table 1**. A large and comparable inter-subject variability was noted for $AUC_{0-\infty}$ and C_{max} with both treatments.

3. Relative bioavailability

$AUC_{0-\infty}$ and C_{max} derived from 16 subjects (56 profiles in total) were considered for relative bioavailability assessment. **Table 2** and **Figure 4** show the main results from the statistical comparison of saquinavir exposure between the two treatments. The intra-subject CV for saquinavir $AUC_{0-\infty}$ and C_{max} were between 22% and 24%.

Figure 3. Pharmacokinetic profiles of saquinavir (mean and standard deviation) after SQV/r (1000/100 mg), taken as Invirase (34 profiles) or SQV_{tablet} (33 profiles)

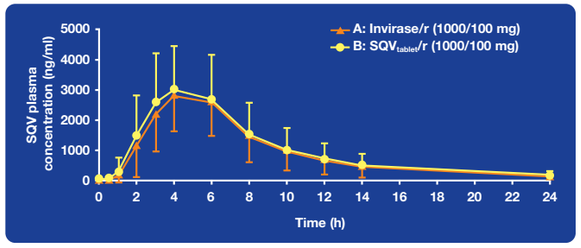


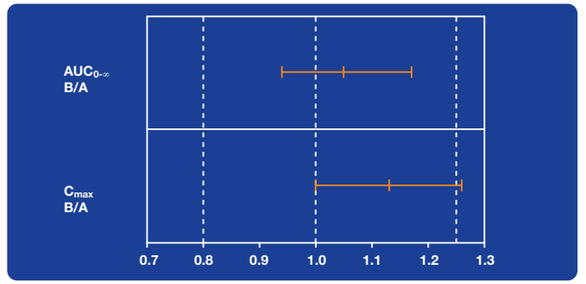
Table 1. Pharmacokinetic parameters of saquinavir after SQV/r (1000/100 mg), taken as Invirase or SQV_{tablet}

Parameter	Invirase/r	SQV_{tablet}/r
number of profiles	34	33
$AUC_{0-\infty}$ (h·ng/ml), geometric mean [CV%]	21,561 [50%]	23,086 [49%]
C_{max} (ng/ml), geometric mean [CV%]	2,982 [42%]	3,369 [43%]
T_{max} (h), median [range]	4 [3–6]	4 [2–6]
$t_{1/2}$ (h), geometric mean [CV%]	5.23 [14%]	5.15 [11%]
CL/F (l/h), geometric mean [CV%]	46.38 [50%]	43.32 [49%]

Table 2. Mean saquinavir exposures and exposure ratios after SQV/r (1000/100 mg), taken as Invirase or SQV_{tablet} (Results based on ANOVA, 16 subjects)

Parameter	Treatment	Geometric mean exposure [CV%]	Exposure ratio (SQV_{tablet}/r:Invirase/r) [90% CI]
$AUC_{0-\infty}$ (h·ng/ml)	Invirase/r	21,433 [58%]	1.05 [0.94–1.17]
	SQV_{tablet}/r	22,460 [52%]	
C_{max} (ng/ml)	Invirase/r	2,930 [48%]	1.13 [1.00–1.26]
	SQV_{tablet}/r	3,298 [46%]	

Figure 4. Mean saquinavir exposure ratios and 90% confidence intervals, after SQV/r (1000/100 mg), taken as Invirase or SQV_{tablet} (Results based on ANOVA, 16 subjects)



Discussion

In the present study, the bioavailability of a new 500 mg tablet formulation of saquinavir mesylate was determined relative to the Invirase 200 mg capsule after a single administration of 1000 mg combined with 100 mg ritonavir *bid*.

As demonstrated, the new formulation exhibits similar bioavailability to Invirase. The mean exposure ratio was 1.05 (90% CI, 0.94–1.17) for $AUC_{0-\infty}$ and 1.13 (1.00–1.26) for C_{max}. Large inter-subject variability was observed in $AUC_{0-\infty}$ and C_{max}, which is well known for saquinavir and related to the effect of CYP3A4 and P-gp on its absorption.[5]

Contrary to previous observations, however, intra-subject variability was moderate with an estimated CV of about 25%. Based on the promising results of this pilot study, a pivotal bioequivalence study will be performed comparing Invirase/r with SQV_{tablet}/r.

The effectiveness of antiretroviral therapy is closely related to adherence[9], which is driven by the convenience and tolerability of the regimen[10]. The smaller size and reduced pill count for the new 500 mg tablet - 6 pills daily in total for *bid* dosing of 1000 mg with 100 mg ritonavir, versus 12 for the 200 mg formulations, could improve treatment success through encouraging better adherence. The new saquinavir 500 mg tablet could replace both the existing Invirase and Fortovase 200 mg capsules.

Conclusion

Roche is developing a new saquinavir 500 mg tablet formulation which shows similar bioavailability to the Invirase 200 mg capsule formulation when dosed at 1000/100 mg in combination with ritonavir.

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