1

Primary Objectives and Study Design

To investigate:

the tolerability and pharmacokinetics of saquinavir-SGC (FORTOVASE ®; FTV) when administered in a once-a-day regimen with a mini dose of Ritonavir (RTV)

Study Design:

single center, open label, randomized, parallel group, sequential study of 5 multidose regimens of either saquinavir-SGC alone or in combination with 100 or 200 mg of RTV administered in the evening with meals for 13 days to a total of 41 healthy volunteers.

2

Table 1: Treatment Regimens

Regimen	Saquinavir-SGC dose	RTV dose
A	1200 mg TID	-
B	1200 mg QD	100 mg QD
C	1600 mg QD	100 mg QD
D	1800 mg QD	100 mg QD
E	1200 mg QD	200 mg QD

Study Design

- Trough blood samples for analysis of plasma saquinavir obtained prior to evening dose on days 2, 7, 11 and 12
- Serial blood samples obtained pre-dose and 1, 2, 3, 4, 6, 8, 12, 18 and 24 hours after the evening dose on day 13.
- Peak saquinavir plasma concentrations (C_{max}), minimum saquinavir concentrations at the end of the dosing interval (C_{min}) were obtained.
- Area under the saquinavir plasma concentration versus time profile for 24 hours (AUC_{24}) was reported. For regimen A the AUC_{24} was calculated as 3 times the AUC for the 8 hour dosing interval.

Table 2: Demographics

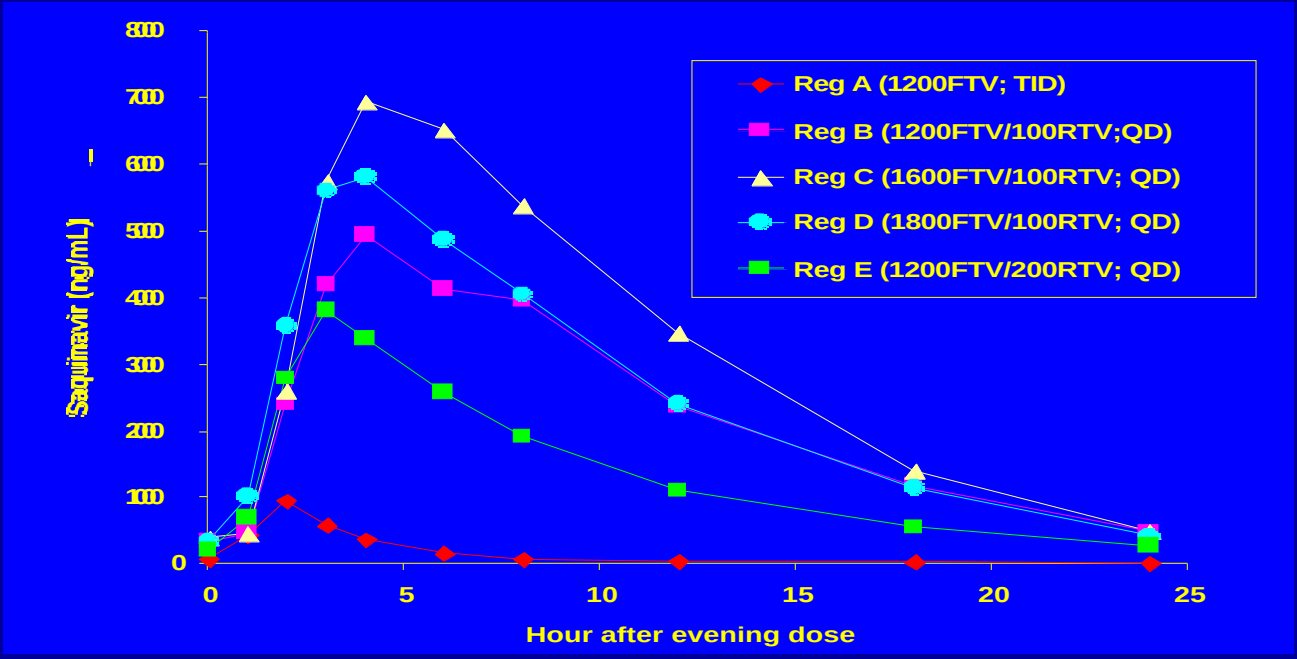
Male /Female	21 / 20
Age (mean, years)	29
Race (%)	
Caucasian	33
African American	8

Table 3: Pharmacokinetic Parameters

Regimen	A	B	C	D	E
n	8	8	9	8	8
Saquinavir SGC Dose (mg)	1200	1200	1600	1800	1200
RTV dose (mg)	0	100	100	100	200
Cmax (µg/mL)	1.0	6.0	7.9	7.5	7.5
Cmin (µg/mL)	0.09	0.5	0.5	0.4	0.3
AUC24 (µg.h/mL)	9.4	58	77	65	34

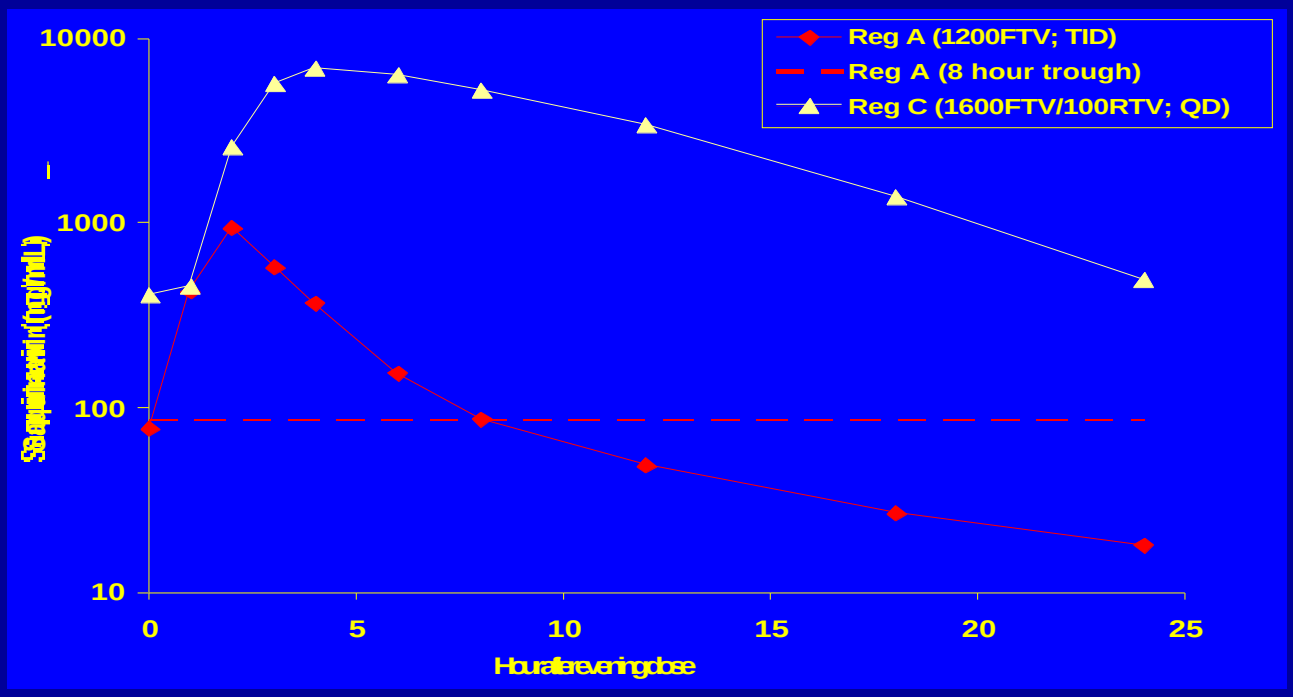
6

Figure 1: Mean (SD) SQV Conc (ng/mL) on Day 13 (Regimens A-E)



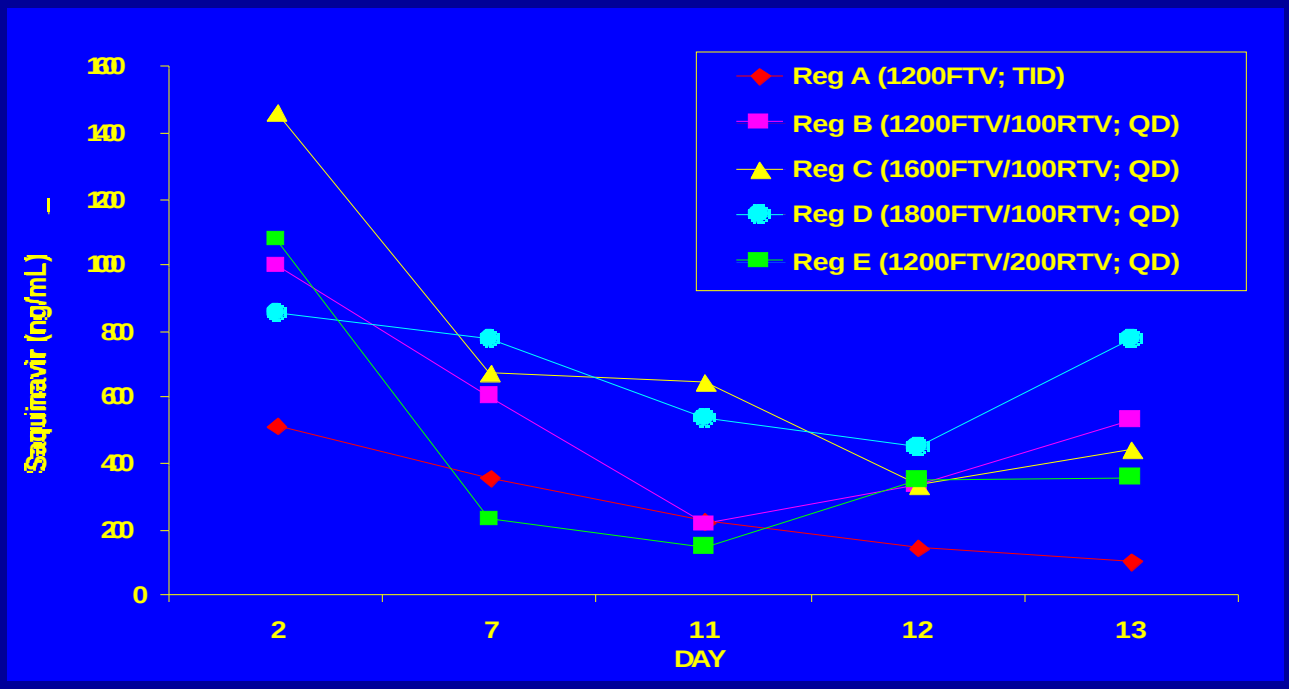
7

Figure 2: Mean (SD) SQV Conc (ng/mL) on Day 13 (Regimens A&C)



8

Figure 3: Mean SQV Trough Levels vs Time (Regimens A-E)



Conclusions

- Saquinavir-SGC in combination with low dose ritonavir yields high saquinavir exposure, even after 24 hours of dosing. Once daily administration of FORTOVASE® in the presence of low 100 mg ritonavir could be a well tolerated, efficacious and convenient treatment choice for HIV patients.

- Saquinavir-SGC alone was well tolerated with no significant adverse events reported.

10

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Favorable Saquinavir Systemic Exposure and Safety of Once Daily Administration of Fortovase® (Saquinavir) Soft Gel Capsule (FTV) in Combination with Low Dose Ritonavir (RTV)

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Introduction

FORTOVASE® (saquinavir soft gelatin capsule; SQV-SGC; FTV) is a potent protease inhibitor (PI) indicated for use in combination with other antiretroviral agents for the treatment of HIV infection.

It is widely accepted that poor adherence to antiretroviral drugs is associated with treatment failure and that more complex regimens tend to be more difficult for patients to adhere to. A once-a-day regimen containing a protease inhibitor would represent a significant advance in the provision of new "patient-friendly" regimens.

The currently approved doses for FTV and RTV in the treatment of HIV infected patients are: 1200 mg TID and 600 mg BID for FTV and RTV respectively. Several studies have demonstrated that ritonavir profoundly inhibits the metabolism of saquinavir leading to greatly increased saquinavir exposure (around 20-fold). It has been proposed that this substantial interaction could be used to alter the dosing frequency of saquinavir from two or three times daily to once a day. To be successful two questions need to be considered: (1) can saquinavir peak exposure (C_{max}) be increased sufficiently and remain well tolerated? And (2) is the saquinavir trough level (C_{trough}) at the end of the 24 hours dose interval sufficiently high enough therapeutically?

Objective

The primary objective of this study was to assess saquinavir plasma exposure and safety with escalating doses of FTV in combination with RTV, and to use these data to select a suitable FTV/RTV combination to be used in an upcoming clinical trial in HIV patients. To ensure adequate saquinavir exposure in HIV patients, a conservative approach in dose selection was anticipated.

Methods

This study was a single center, open label, randomized, parallel group, sequential study of several multi-dose regimens of either FTV alone or FTV in combination with RTV in healthy volunteers. Volunteers (8/regimen) were randomized to receive one of 5 different multiple dose regimens (Table 1) following a standard meal (approximately 900 kcalories with 35% fat) for 13 days starting from evening of day 1. A total of 45 subjects were randomized, 41 subjects contributed PK data and 40 subjects completed treatment. Patient demographics are shown in Table 2.

Trough blood samples for analysis of plasma saquinavir and RTV were obtained prior to evening doses on days 2, 7, 11 and 12. Serial blood samples were obtained at pre-dose and 1, 2, 3, 4, 6, 8, 12, 18 and 24 after the evening dose on day 13. Trough plasma concentrations (C_{trough}), peak plasma concentration (C_{max}), the area under the plasma concentration time curve for one dosing day (AUC_{24h}) were evaluated.

Results

Compared to arm A, the addition of RTV elevated saquinavir exposure by 300-800%, delayed Tmax by 1-3 hours (2h vs. 3-6h) and reduced variability of Cmax, Cmin and AUC_{24h} by half (C.V: 88-106% vs. 42-64%) (Table 3, Figure 1 & 2). Overall, there was no proportional increase in saquinavir exposure with respect to higher FTV or RTV doses. However, arm C appeared to have higher saquinavir exposure, while arm E the lowest. Trough concentrations of saquinavir were 5.5 fold higher for arm C compared to trough concentrations for arm A (Figure 2).

Evaluation of trough concentration over time (Figure 3) suggests that steady state pharmacokinetics were reached by approximately day 11.

All regimens were well tolerated with no significant adverse events, or grade 3 or 4 toxicity reported. The FTV alone, FTV/RTV combination regimens were well tolerated with no significant adverse events reported. It appeared that the administration of RTV solution to healthy volunteers was reasonably well tolerated.

Conclusions

The data suggests that FORTOVASE® in combination with low dose ritonavir yields high saquinavir exposure, even after 24 hours of dosing. Once daily administration of FORTOVASE® in the presence of low 100 mg ritonavir could be a well tolerated, efficacious and convenient treatment choice for HIV patients.

FORTOVASE® alone was well tolerated with no significant adverse events reported.