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Background

- Combination therapy with SQV/ATV may offer a number of advantages over current protease inhibitor (PI) based therapy including significant antiviral potency, a complex genetic barrier to resistance, once daily dosing and low risk of lipid abnormalities.
- In vitro, SQV and ATV is synergistic in peripheral blood mononuclear cells infected with HIV-1 (1)
- PK data with combinations of SQV/ATV suggested that ATV boosts SQV while SQV has little to no effect on ATV (2). No data is available on the interaction between ATV and the preferred hard capsule formulation of SQV nor has a comparison of SQV plasma concentrations been made to concentrations achieved using boosted SQV.

The combination of SQV/ATV has been reported in at least two trials:
A124-009 prospectively randomized treatment-experienced patients to receive either SQV/ATV 1200/400mg QD, SQV/ATV 1200/600mg QD or SQV/RTV 400/400mg BID with two nucleoside reverse transcriptase inhibitors (NRTI). The mean change from baseline in viral load (VL) at week 48 was -1.44, -1.19 and -1.66 log₁₀ copies/mL, respectively. The proportion of patients with VL <400 copies/mL was 41%, 29% and 35%, respectively. Mean CD4 cell increase from baseline was 109, 55 and 149 cells/mm³, respectively (3)

A124-045 prospectively randomized treatment-experienced patients with virologic failure on two or more regimens to receive tenofovir (TDF) with one other NRTI and either SQV/ATV 1200/400mg QD, ATV/RTV 300/100mg QD or lopinavir/RTV 400/100mg BID. The SQV/ATV arm was terminated prematurely due to inferior efficacy in this arm compared with the other two arms. Nevertheless, at week 48 the mean change in viral load was -1.54 log₁₀ copies/mL with 36% and 24% of patients achieving VL <400 and <50 copies/mL, respectively (4). The suboptimal response in this arm may be attributed to a drug interaction between ATV and TDF where sub-therapeutic concentrations of ATV may have occurred due to the improper dosing of SQV when combined with ATV (5-6)

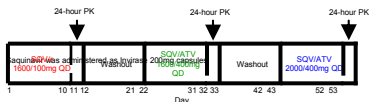
Objective

- To evaluate the steady-state pharmacokinetics and short-term safety of SQV/ATV 1600/400 and 2000/400mg QD in seronegative volunteers using the hard capsule formulation of SQV.
- To evaluate possible differences in pharmacokinetics between males and females.

Methods

- ASPIRE I is a prospective, open-label, three-way sequential crossover clinical trial in seronegative volunteers.
- 16 subjects between the ages of 18 and 65 years old were selected to participate. A sample size of 16 has 90% power to demonstrate a statistically significant difference of 33% in SQV AUC at the 5% alpha level assuming 40% intrasubject variability in AUC. Subjects were enrolled such that the numbers of males and females participating would be balanced. Enrollment would continue until all 16 subjects had completed all 3 PK assessments.

Study medications were administered in the following manner:



PK Assessment

- On days 11, 32 and 53 blood was drawn pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours post dose following ingestion of study medications. A standardized breakfast was given on the morning of each PK assessment day.
- PI plasma concentrations were determined by a fully validated method using high performance liquid chromatography with UV detection.
- PK parameters were determined by noncompartmental analysis using WinNonlin 4.0 (Pharsight Corporation, Mountain View, CA, USA). The area under the plasma concentration time curve (AUC₀₋₂₄) was calculated using the linear trapezoidal rule and the slope of the terminal part of the plasma concentration-time curve was obtained by linear regression after semi logarithmic transformation.

Safety Assessment

- Routine laboratory parameters including liver function tests and lipid profiles, physical examinations and vital signs were evaluated on days 11, 32 and 53. A follow-up assessment was made 1 month post study conclusion.

Results

- Seventeen healthy subjects were enrolled and 15 (8 males, 7 females) completed all three PK assessments. Two subjects enrolled discontinued before finishing the second and third round respectively both due to a hypersensitivity reaction probably related to study medication.

Median (range) baseline demographics for the study population were as follows:

	Entire cohort	Males	Females
N	15	8	7
Age (years)	36 (22-46)	40.5 (22-46)	27 (22-36)
Weight (kg)	75.5 (55-95)	85.5 (65-110)	55.5 (45-75)

Summary of median (range) steady-state pharmacokinetic parameters are summarized in Table 1.

Table 1: Summary of median (range) steady-state pharmacokinetic parameters for SQV, ATV and RTV

	C ₀ (ng/mL)	T _{1/2} (hr)	T _{1/2} (hr)	C ₀ (ng/mL)	AUC ₀₋₂₄ (ng·hr/mL)
SQV 1600mg + RTV 100mg	252.3 (198.5-325.7)	4.6 (3.3-6.6)	2.1 (1.9-2.6)	27.7 (16.2-59.1)	26.2 (13.3-58.1)
1600mg + ATV 400mg	160.2 (104.1-237.5)	5.8 (3.8-8.8)	2.0 (1.9-2.2)	31.0 (17.0-51.4)	17.2 (11.2-29.4)
2000mg + ATV 400mg	249.3 (164.4-385.8)	5.8 (3.8-8.8)	2.0 (1.9-2.2)	32.3 (17.1-51.5)	18.1 (12.2-32.9)
RTV 100mg + SQV 1600mg	102.2 (66.1-154.3)	5.8 (3.8-8.8)	2.0 (1.9-2.2)	12.6 (6.8-21.7)	52.1 (32.9-84.5)
RTV 100mg + SQV 2000mg	103.9 (67.5-152.1)	5.8 (3.8-8.8)	2.0 (1.9-2.2)	12.6 (6.8-21.7)	52.1 (32.9-84.5)

RTV 100mg + SQV 1600mg and RTV 100mg + SQV 2000mg were given as a single dose. SQV AUC₀₋₂₄ was approximately 4x and 2.5 greater with SQV/RTV 1600/100 and 2000/100mg QD, respectively, suggesting no apparent effect of SQV on ATV.

RTV PK parameters were also comparable to historic parameters (8)

Figure 1: Mean (standard deviation) plasma concentration-time profiles for SQV and ATV

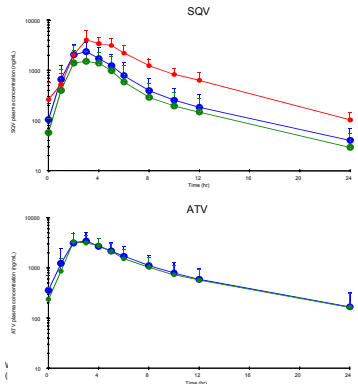


Table 1

	Males		Females	
	C ₀ (ng/mL)	AUC ₀₋₂₄ (ng·hr/mL)	C ₀ (ng/mL)	AUC ₀₋₂₄ (ng·hr/mL)
SQV 1600mg + RTV 100mg	167.2 (104.4-274.8)	15.2 (10.5-41)	16.5 (11.41-138.2)	0.22 (0.24-0.65)
1600mg + ATV 400mg	102.1 (66.1-154.3)	5.8 (3.8-8.8)	31.0 (17.0-51.4)	0.14 (0.11-0.18)
2000mg + ATV 400mg	177.0 (112.1-274.8)	15.2 (10.5-41)	32.3 (17.1-51.5)	0.14 (0.11-0.18)
ATV 400mg + SQV 1600mg	12.6 (6.8-21.7)	52.1 (32.9-84.5)	12.6 (6.8-21.7)	52.1 (32.9-84.5)
ATV 400mg + SQV 2000mg	12.6 (6.8-21.7)	52.1 (32.9-84.5)	12.6 (6.8-21.7)	52.1 (32.9-84.5)

Safety

- Grade 3 hyperbilirubinemia was observed in 0, 2, and 7 subjects during periods 1, 2 and 3, respectively. Grade 3 GI disturbances were reported in 7, 3 and 4 subjects during periods 1, 2 and 3, respectively. Hypertension was not observed in any subject.

Discussion

Combining two PIs at pharmacologically active concentrations (i.e. dual PI therapy) is an attractive option for both naive and treatment-experienced HIV-infected patients. Previous studies have suggested the threshold for pharmacologic activity with SQV is an AUC₀₋₂₄ >10 mg·hr/mL (9). In this study, SQV combined with ATV did not achieve the plasma concentrations of boosted SQV confirming the potency of low-dose RTV on SQV metabolism. SQV/ATV 2000/400mg QD achieved a median SQV AUC₀₋₂₄ of 10.6 mg·hr/mL. However, 2 of 7 female subjects and 5 of 8 male subjects had SQV AUC₀₋₂₄ <10 mg·hr/mL. There was no apparent effect of SQV on ATV plasma concentrations. Patients with no previous exposure to PIs and who cannot tolerate RTV may benefit from a combination of SQV/ATV but therapeutic drug monitoring may be warranted. Of note, the interaction with TDF was not assessed in this study.

Interestingly, women had significantly higher exposure to all 3 PIs. This effect was still apparent even after adjusting for body weight. Differences in PK between sexes have previously been reported with SQV and RTV (10-11). No sex related PK differences have been reported for ATV.

Further studies of SQV/ATV combinations both QD and BID are warranted to examine the possibility of achieving therapeutic SQV levels without the use of low-dose RTV.

Conclusions

- RTV significantly increases SQV concentrations relative to the combination of SQV and ATV. SQV doses of 1600 and 2000mg do not alter ATV concentrations.
- Sex appears to influence exposure to all three PIs.
- SQV/ATV 2000/400mg QD reaches pharmacologically active exposure for both PIs and should be further evaluated in HIV-infected, PI-naive subjects for PK, efficacy and tolerability.

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