Poster 586

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Pharmacokinetics (PK) of Twice Daily (BID) Saquinavir Tablet (SQV) with Low-Dose Ritonavir (RTV) or Full-Dose Atazanavir (ATV) in Seronegative Volunteers: ASPIRE II

Jennifer R. King[1], Sunita Paul Lundy[2], Thomas N. Kakuda[3], Stephen L. Becker[4], Man Ming Tse[5], F. Lisa Sterman[5], and Edward P. Acosta[1]
[1]University of Alabama at Birmingham, Birmingham, AL, [2]PPD, Menlo Park, CA, [3]Tibotec, Inc., Yardley PA, [4]AnorMED, Inc., Langley, BC [5]Pacific Horizon Medical Group, San Francisco CA.,

Jennifer R. King, Pharm.D.
University of Alabama at Birmingham
1530 3rd Ave S. VH 101A
Birmingham, AL 35294
Office: (205) 934-2696
Fax: (205)-934-6201
E-mail: jennifer.king@ccc.uab.edu

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 and low risk of lipid abnormalities.
- In vitro, SQV and ATV are synergistic in peripheral blood mononuclear cells infected with HIV.(1)
- PK data with combinations of SQV/ATV suggest that ATV boosts SQV while SQV has little to no effect on ATV.(2)
- ASPIRE I examined the pharmacokinetics of once daily SQV hard capsules with low-dose RTV or full dose ATV in seronegative volunteers. RTV significantly increased SQV concentrations relative to the combination of SQV and ATV, SQV doses of 1600 and 2000mg did not alter ATV concentrations, sex appeared to influence exposure to all three PIs and SQV/ATV 2000/400mg QD reached pharmacologically active exposure for both PIs. (3)
- No data are available on the interaction between ATV and SQV dosed twice daily.

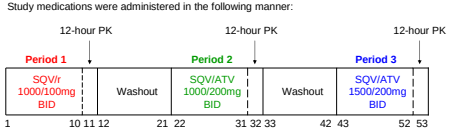
Objective

- To evaluate the steady-state pharmacokinetics and short-term safety of SQV/RTV 1000/100, SQV/ATV 1000/200 and 1500/200mg BID in seronegative volunteers using the SQV 500mg tablet formulation
- To evaluate possible differences in pharmacokinetics between males and females

Methods

Study Design

- ASPIRE II 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 saquinavir AUC at the 5% alpha level assuming 40% intraindividual 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:



- Saquinavir was administered as the 500mg tablet.

PK Assessment

- On days 11, 32 and 53 blood was drawn pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours post dose following observed 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. The lower limit of quantitation was 25 ng/mL.
- 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 (AUC_{12}) was calculated using the linear-log trapezoidal rule and the slope of the terminal part of the plasma concentration-time curve was obtained by linear regression after semi logarithmic transformation. The estimated AUC_{24} ($EstAUC_{24}$) was calculated as twice the AUC_{12}.

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

- Sixteen healthy subjects enrolled (8 males, 8 females) and completed all three PK assessments.
- Median (range) baseline demographics for the study population were as follows:

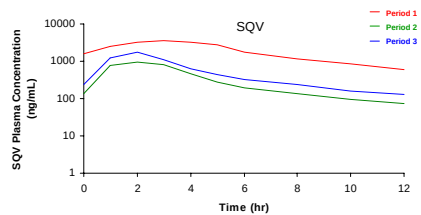
	Entire cohort	Males	Females
N	16	8	8
Age (years)	35.5 (23-52)	42.5 (23-52)	32 (23-36)
Weight (kg)	79.3 (54.5-93.6)	84.8 (64.1-93.6)	62.3 (54.5-84.5)

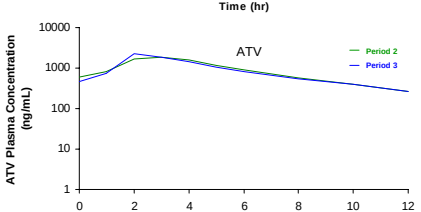
Steady-state Pharmacokinetics

- Median (range) SQV, ATV and RTV steady-state pharmacokinetic parameters are summarized in Table 1 and median plasma SQV and ATV concentration-time profiles are shown in Figure 1.
- **Table 1:** Summary of median (range) steady-state pharmacokinetic parameters for SQV, ATV and RTV

	C_{max} (ng/mL)	T_{12} (hr)	T_{max} (hr)	C_{12h} (ng/mL)	AUC_{12} (hour•ng/L)
SQV					
Period 1: SQV 1000mg + RTV 100mg	4065.7 (723.3-14980.0)	4.1 (2.5-7.4)	2.5 (1.0-4.1)	599.4 (32.2-4203.2)	24.7 (2.5-101.7)
Period 2: SQV 1000mg + ATV 200mg	1322.0 (260.6-5687.3)	4.4 (2.5-11.0)	2.0 (1.0-4.0)	74.8 (31.5-1652.1)	4.03 (1.3-21.4)
Period 3: SQV 1500mg + ATV 200mg	1887.8 (370.4-5348.1)	4.3 (2.0-13.8)	1.5 (1.0-4.0)	129.35 (12.5-424.9)	7.6 (1.8-22.9)
ATV					
Period 2: ATV 200mg + SQV 1000mg	2271.8 (595.0-4709.5)	3.6 (2.4-6.0)	3.0 (2.0-5.1)	264.6 (93.1-603.9)	12.6 (3.6-20.8)
Period 3: ATV 200mg + SQV 1500mg	2557.0 (511.4-3829.0)	3.8 (2.6-5.3)	3.0 (1.0-4.0)	262.2 (85.9-580.4)	11.4 (3.0-19.7)
RTV					
Period 1: RTV 100mg + SQV 1000mg	1892.5 (358.1-6105.3)	3.4 (2.0-5.4)	2.5 (1.0-4.1)	254.8 (70.00-930.4)	10.2 (2.4-32.1)

- SQV C_{max}, C_{12h} and AUC_{12} were significantly higher in period 1 compared to 2 or 3 ($p<0.05$ for all comparisons).
- ATV PK parameters were similar between periods 2 and 3. ATV $EstAUC_{24}$ (25.2 mg·h/L for Period 1, 22.8 mg·h/L for Period 2) were comparable to AUC_{24} from seronegative historical controls receiving ATV 400mg QD (29.4 mg·h/L) (4).
- **Figure 1:** Median plasma concentration-time profiles for SQV and ATV





- Women had significantly higher C_{max} and AUC_{12} for all 3 PIs compared to men after adjusting for weight ($p<0.05$).

	Males		Females	
	C_{max}/wt (ng/mL/kg)	AUC/wt (hour•ng/L/kg)	C_{max}/wt (ng/mL/kg)	AUC/wt (hour•ng/L/kg)
SQV				
Period 1: SQV 1000mg + RTV 100mg	24.6 (9.0-52.5)	0.16 (0.03-0.34)	95.4 (70.4-209.2)	0.65 (0.46-1.43)
Period 2: SQV 1000mg + ATV 200mg	8.9 (2.8-18.5)	0.03 (0.01-0.06)	29.8 (18.4-66.5)	0.1 (0.06-0.25)
Period 3: SQV 1500mg + ATV 200mg	13.6 (4.0-35.3)	0.06 (0.02-0.12)	38.1 (22.4-62.3)	0.15 (0.08-0.27)
ATV				
Period 2: ATV 200mg + SQV 1000mg	19.3 (6.5-34.8)	0.09 (0.04-0.22)	39.1 (26.5-76.7)	0.21 (0.15-0.27)
Period 3: ATV 200mg + SQV 1500mg	18.7 (5.6-46.2)	0.09 (0.03-0.24)	45.4 (29.2-55.2)	0.23 (0.14-0.31)
RTV				
Period 1: RTV 100mg + SQV 1000mg	13.9 (4.0-26.8)	0.09 (0.03-0.17)	46.3 (22.6-103.3)	0.27 (0.13-0.54)

Safety

- Grade 3 or 4 hyperbilirubinemia was observed in 0, 6, and 2 subjects during periods 1, 2, and 3, respectively. Grade 3 GI disturbances were reported in 1 subject during period 1. Hyperlipidemia was not observed in any subject.

Discussion

- Combining two PIs to achieve pharmacologically active concentrations is an attractive option for both naïve and treatment-experienced HIV-infected patients. Previous studies have suggested the threshold for pharmacologic activity with SQV is an AUC_{24} >10 mg·h/L.(5) In this study, SQV/RTV 1000/100mg BID produced a median SQV $EstAUC_{24}$ of 49.4 mg·h/L. SQV/ATV did not achieve plasma concentrations comparable with SQV/RTV. However, SQV/ATV 1500/200mg achieved a median SQV $EstAUC_{24}$ of 15.2 mg·h/L. The estimated protein-binding corrected IC_{95} for SQV is ~100 ng/mL. SQV concentrations >100 ng/mL were achieved in 75% of subjects receiving SQV/ATV 1500/200mg. The median SQV C_{12h} was 264.6 ng/mL There was no apparent effect of SQV on ATV plasma concentrations. PI-naive patients and those who cannot tolerate RTV may benefit from a combination of SQV/ATV but therapeutic drug monitoring may be warranted.
- These are the first pharmacokinetic data of ATV administered twice daily; however, the safety and efficacy of this regimen have not been studied in patients. ATV C_{max} was ~ 55% lower compared with ATV 400mg qd and ATV C_{12h} was ~ 96% higher than ATV C_{24h} after once-daily dosing. (6)
- 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. (3, 5, 7-8)
- Further studies of SQV/ATV 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. As expected, SQV doses do not alter ATV concentrations.
- Sex appears to influence exposure to all three PIs.
- SQV/ATV 1500/200mg BID reaches pharmacologically active exposure for both PIs and should be further evaluated in HIV-infected, PI-naïve subjects for PK, efficacy and tolerability.

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