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Assessment of the Steady-State Pharmacokinetic Interaction of Lopinavir/ritonavir with Either Indinavir or Saquinavir in Healthy Subjects

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ABSTRACT

Objectives: To assess the effect of multiple doses of LPV/r 400/100 mg BID on the pharmacokinetics of SQV and IDV. The pharmacokinetics of LPV/r in the presence of SQV and IDV were also determined.

Methods: Healthy subjects (n=28) were randomized to SQV 1200 mg TID or IDV 800 mg TID on Days 1-5. LPV/r 400/100 mg BID was co-administered with either IDV 600 mg BID or SQV 800 mg BID on Days 6-15. Ten subjects in SQV arm also received SQV 1200 mg BID + LPV/r on Days 16-20. Plasma samples were collected over a dosing interval on Days 5 and 15, and on Day 20 in SQV arm. Noncompartmental PK methods were used. Effect of co-administration was assessed by ANOVA.

Results: IDV 600 mg BID + LPV/r produced lower IDV C_{max}, similar AUC_{24} and higher C_{min} relative to IDV 800 mg TID. Ratio of central values (RCV), (90% CI) for IDV C_{max} was 0.71 (0.63, 0.81), AUC_{24} 0.91 (0.75, 1.10) and C_{min} 3.47 (2.59, 4.63); median IDV C_{trough}/protein-binding-adjusted IC_{50} for *wt*-HIV (IQ) increased from 4.4 to 11. SQV concentrations with SQV 800 mg BID + LPV/r were substantially higher vs. SQV 1200 mg TID. RCV for SQV C_{max} was 6.3, AUC_{24} 9.6 and C_{min} 16.7; SQV median IQ increased from 0.27 to 5.2. SQV concentrations were similar with 800 and 1200 mg BID + LPV/r; RCV (90% CI) for both C_{max} and AUC was 1.00 (0.82, 1.23) and for C_{min} 1.04 (0.82, 1.32). LPV concentrations were similar to historical; median LPV IQ was 99 with SQV and 95 with IDV.

Conclusions: 1) IDV 600 mg BID + LPV/r produced a 3.5x higher IDV C_{min}, similar AUC and lower C_{max} *vs.* IDV 800 mg TID. 2) SQV C_{min} was 16.7x higher during SQV 800 mg BID + LPV/r compared to SQV 1200 mg TID. 3) SQV 800 and 1200 mg BID + LPV/r produced similar SQV concentrations; lower SQV dosing regimens with LPV/r are being explored.

INTRODUCTION

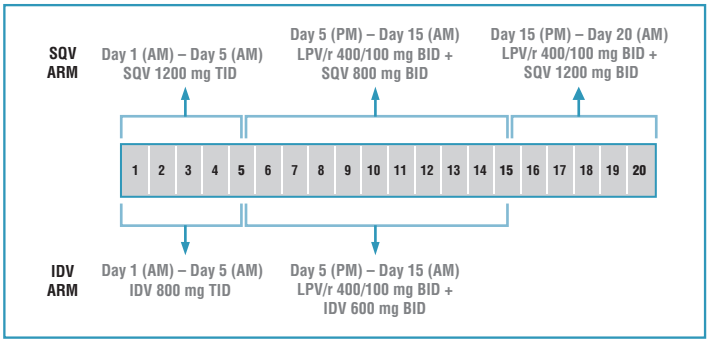
- Kaletra® (Lopinavir/ritonavir or LPV/r), Fortovase® (Saquinavir or SQV) and Crixivan® (Indinavir or IDV) are HIV protease inhibitors approved worldwide for treatment of HIV in combination with other antiretrovirals.
- Approved clinical adult dose of LPV/r is 400/100 mg BID; SQV is 1200 mg TID; IDV is 800 mg TID.
- At clinical concentrations, LPV/r, IDV and to a lesser extent SQV inhibit CYP3A-mediated metabolism; LPV/r is also a metabolic inducer.
- Multiple-dose LPV/r has been shown to substantially increase single-dose SQV and IDV trough concentrations.

OBJECTIVE

- To assess the effect of multiple doses of LPV/r 400/100 mg BID on the pharmacokinetics of SQV and IDV.
- The pharmacokinetics of LPV/r in the presence of SQV and IDV were also determined.

STUDY DESIGN

- Multiple-dose, open-label, single-center, non-fasting study.
- Healthy male and female subjects (N=28) were enrolled and equally randomized into an SQV or IDV dosing arm.
- Subjects received standardized meals containing ~ 30% of calories from fat.
- All PIs given with food except IDV 800 mg TID alone was taken on empty stomach.
- Intensive pharmacokinetic sampling for study drug concentrations occurred on Study Days 5, 15, and 20.



METHODS

- Plasma samples were collected pre-dose and at 1, 2, 3, 4, 6 and 8 hours post dose, Study Day 5 for IDV or SQV.
- Plasma samples were collected pre-dose and at 1, 2, 3, 4, 6, 8, 10 and 12 hours post dose, Study Day 15 for LPV/r and SQV or IDV and Study Day 20 (SQV arm only) for LPV/r and SQV.
- Additional pre-dose (trough) plasma samples were collected on Study Days 3, 11, 13 and 18.
- LPV, RTV, SQV and IDV concentrations measured by LC/MS/MS.
  - LPV and SQV limit of quantitation (LOQ) = 5.0 ng/mL
  - RTV and IDV LOQ = 1.0 ng/mL
- Noncompartmental methods were used to calculate pharmacokinetic parameters.
- Effect of LPV/r on SQV or IDV as well as effect of two dosing regimens of SQV on LPV/r were assessed by paired t-test on log-transformed parameters.
- 90% confidence intervals for the bioavailability of the regimens were obtained for log-transformed C_{max}, C_{min}, C_{trough} and AUC.
- A repeated measures analysis was performed on log-transformed C_{trough} of IDV, SQV, LPV and RTV.

METHODS

Demographics

- 14 subjects completed dosing in the SQV arm through Day 15; 10 subjects continued through Day 20.
- 13 subjects completed dosing in the IDV arm.

	SQV Arm N=14	IDV Arm N=13
Age (yrs)	31 (20 - 48)	34 (19 - 55)
Weight (kg)	83 (66 - 99)	75 (55 - 93)
Height (cm)	177 (158 - 184)	174 (154 - 176)
Race	8 Caucasian, 5 Black, 1 Asian	12 Caucasian, 1 Black
Gender	12 Male, 2 Female	9 Male, 4 Female

Age, weight and height presented as mean (range)

RESULTS

Table 1. Effect of LPV/r on Saquinavir PK (Mean ± SD)

	Day 5 SQV 1200 mg TID (N=14)	Day 15 SQV 800 mg BID and LPV/r (N=14)	Day 20 SQV 1200 mg BID and LPV/r (N=10)
C_{max} (µg/mL)	0.41 ± 0.18	2.53 ± 0.77*	2.49 ± 1.39*
T_{max} (h)	2.4 ± 0.6	3.5 ± 1.1	3.8 ± 1.0*
C_{min} (µg/mL)	0.05 ± 0.02	0.90 ± 0.35*	0.76 ± 0.33*
C_{trough} (µg/mL)	0.08 ± 0.05	1.39 ± 0.73*	1.02 ± 0.50*
IQ+#	0.28	5.24	4.54
	(0.08 - 0.88)	(1.46 - 13.49)	(1.33 - 8.07)
AUC_{24} (µg•h/mL)†	4.05 ± 1.70	37.9 ± 11.7*	35.1 ± 17.3*
$t_{1/2}$^	1.89 ± 0.28	5.65 ± 1.60*	5.12 ± 1.35*
CL/F+	1041 ± 409	47.5 ± 19.5	84.4 ± 41.9

* Statistically significantly different from reference (Study Day 5, pair tested, p<0.05).
\+ Parameter not tested statistically.
\# IQ (inhibitory quotient) is based on saquinavir C_{trough}/protein binding-adjusted *wt*-HIV = 0.25 µg/mL[4]; presented as median (range).
^ Presented as harmonic mean and pseudostandard deviation; statistical tests based on β; calculated from C_{max} to C_{12h}.
† AUC_{24} was estimated from the calculated AUC over a dosing interval.

Table 2. Relative Bioavailability of Saquinavir

Study Day* Test *vs.* Reference	Pharmacokinetic Parameter	Central Values Test	Central Values Reference	Relative Bioavailability Point Estimate	Relative Bioavailability 90% Confidence Interval
15 *vs.* 5	C_{max} (µg/mL)	2.4	0.4	6.339	5.320 - 7.552
	C_{min} (µg/mL)	0.8	0.0	16.743	13.731 - 20.416
	C_{trough} (µg/mL)	1.2	0.1	17.425	14.258 - 21.296
	AUC_{24} (µg•h/mL)	35.9	3.7	9.619	8.051 - 11.492
20 *vs.*15	C_{max} (µg/mL)	2.2	2.2	0.978	0.736 - 1.299
	C_{min} (µg/mL)	0.7	0.7	0.950	0.698 - 1.293
	C_{trough} (µg/mL)	0.9	1.0	0.883	0.626 - 1.246
	AUC_{24} (µg•h/mL)	31.6	32.6	0.969	0.731 - 1.284

*Day 5 - SQV 1200 mg TID; Day 15 - SQV 800 mg BID + LPV/r 400/100 mg BID; Day 20 - SQV 1200 mg BID + LPV/r 400/100 mg BID.

Figure 1. Saquinavir Mean (SD) Concentration-Time Profiles

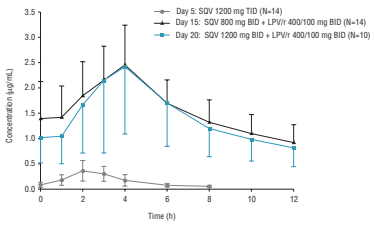


Figure 2. Saquinavir AUC_{24} Values

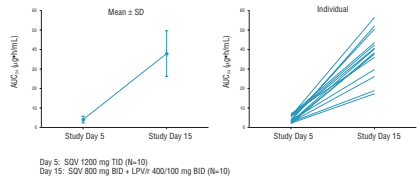


Figure 3. Saquinavir C_{min} Values

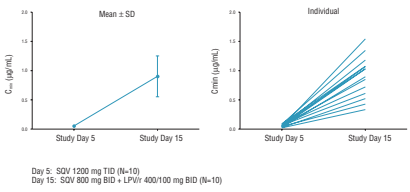
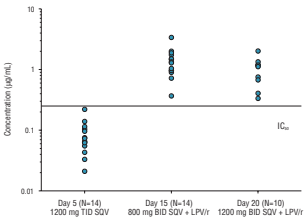


Figure 4. Saquinavir C_{trough} Relative to *wt*-HIV IC_{50}[4]



RESULTS

Table 3. Effect of LPV/r on Indinavir PK (Mean ± SD)

	Day 5 IDV 800 mg TID (N=13)	Day 15 IDV 600 mg BID and LPV/r (N=13)
C_{max} (µg/mL)	7.73 ± 2.72	5.33 ± 1.14*
T_{max} (h)	1.1 ± 0.3	2.7 ± 0.6*
C_{min} (µg/mL)	0.20 ± 0.18	0.64 ± 0.43*
C_{trough} (µg/mL)	0.28 ± 0.24	0.80 ± 0.56*
IQ+#	4.35	11.2
	(1.64 – 18.69)	(6.1 – 41.9)
AUC_{24} (µg•h/mL)†	67.7 ± 31.3	58.1 ± 17.2
$t_{1/2}$^	1.21 ± 0.15	2.93 ± 0.49
CL/F^	42.8 ± 19.0	22.0 ± 5.1

* Statistically significantly different from reference (Study Day 5, pair tested, p<0.05).
\+ Parameter not tested statistically.
\# IQ (inhibitory quotient) is based on C_{trough}/indinavir protein binding-adjusted *wt*-HIV = 0.053 µg/mL[4]; presented as median (range).
^ Presented as harmonic mean and pseudostandard deviation; statistical tests based on β; calculated from C_{max} to C_{12h}.
† AUC_{24} was estimated from the calculated AUC over a dosing interval.

Table 4. Relative Bioavailability of Indinavir

Study Day* Test *vs.* Reference	Pharmacokinetic Parameter	Central Values Test	 Reference	Relative Bioavailability Point Estimate	 90% Confidence Interval
15 *vs.* 5	C_{max} (µg/mL)	5.2	7.3	0.714	0.626 - 0.814
	C_{min} (µg/mL)	0.6	0.2	3.466	2.595 - 4.635
	C_{trough} (µg/mL)	0.7	0.2	3.002	2.325 - 3.879
	AUC_{24} (µg•h/mL)	56.1	61.6	0.911	0.754 - 1.102

*Day 5 – IDV 800 mg TID; Day 15 – IDV 600 mg BID + LPV/r 400/100 mg BID.

Figure 5. Indinavir Concentration-Time Profiles

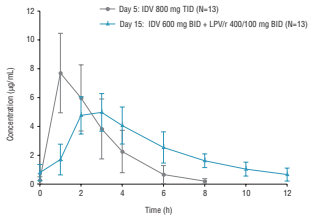


Figure 6. Indinavir Mean (SD) AUC_{24} Values

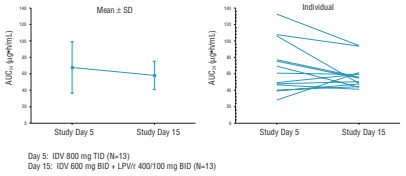


Figure 7. Individual Indinavir C_{min} Values

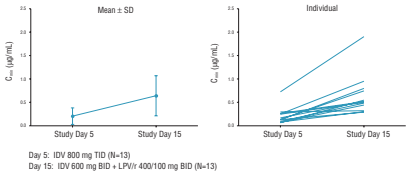


Figure 8. Indinavir C_{trough} Relative to IC_{50}[4]

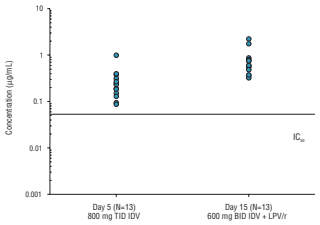


Table 5. Lopinavir PK (Mean ± SD) During Saquinavir and Indinavir

	Day 15 IDV 600 mg BID and LPV/r (N=13)	Day 15 SQV 800 mg BID and LPV/r (N=14)	Day 20 SQV 1200 mg BID and LPV/r (N=10)
C_{max} (µg/mL)	11.57 ± 2.52	11.06 ± 2.25	10.26 ± 2.09
T_{max} (h)	4.6 ± 1.0	4.6 ± 1.1	5.2 ± 1.0
C_{min} (µg/mL)	5.92 ± 3.11	5.75 ± 2.05	5.11 ± 1.49
C_{trough} (µg/mL)	6.71 ± 3.57	7.12 ± 2.32	6.55 ± 2.15
IQ+#	95	99	86
	(11-193)	(45 – 154)	(56 – 168)
AUC_{24} (µg•h/mL)†	208.0 ± 59.3	197.4 ± 43.3	179.7 ± 37.4
$t_{1/2}$^	9.20 ± 4.83	8.74 ± 2.78	8.07 ± 1.94
CL/F^	4.25 ± 1.73	4.25 ± 0.99	4.62 ± 0.94

\# IQ (inhibitory quotient) is based on lopinavir C_{trough}/protein binding-adjusted *wt*-HIV = 0.07 µg/mL[4]; presented as median (range).
^ Presented as harmonic mean and pseudostandard deviation; calculated from C_{max} to C_{12h}.
† AUC_{24} was estimated from the calculated AUC over a dosing interval.

RESULTS

Table 6. Relative Bioavailability of Lopinavir During Saquinavir Dosing Regimens

Study Day* Test *vs.* Reference	Pharmacokinetic Parameter	Central Values Test	Central Values Reference	Relative Bioavailability Point Estimate	Relative Bioavailability 90% Confidence Interval
20 *vs.* 15	C_{max} (µg/mL)	10.1	10.6	0.950	0.847 - 1.065
	C_{min} (µg/mL)	4.9	5.1	0.957	0.818 - 1.121
	C_{trough} (µg/mL)	6.3	6.2	1.016	0.879 - 1.175
	AUC_{24} (µg•h/mL)	176.3	184.1	0.958	0.854 - 1.073

*Day 15 – SQV 800 mg BID + LPV/r 400/100 mg BID; Day 20 – SQV 1200 mg BID + LPV/r 400/100 mg BID.

Figure 9. Lopinavir Mean (SD) Concentration-Time Profiles

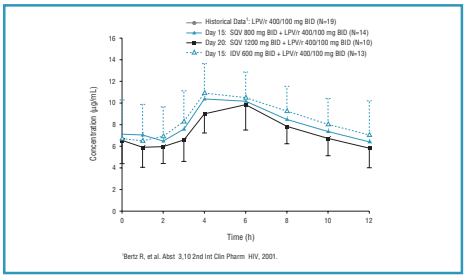


Figure 10. Ritonavir Mean (SD) Concentration-Time Profiles

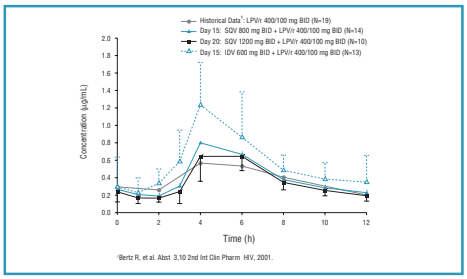
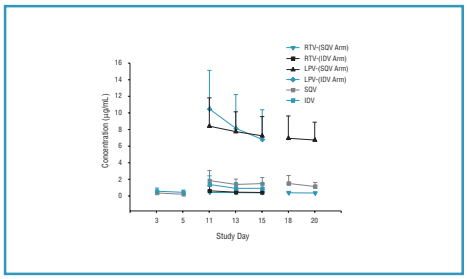


Figure 11. Mean (SD) Trough Concentrations, Shown by Day



Pre-dose Trough Evaluation for Attainment of Steady-State

Saquinavir

- When dosed alone at 1200 mg TID, saquinavir trough appeared to decrease from Day 3 to Day 5 (p=0.0025); since SQV is not a metabolic inducer, it is expected that SQV will be at steady state after 3-4 days of dosing.
- SQV appears to approach steady state by Study Day 15, after 10 days of combination therapy at a dose of 800 mg BID with LPV based on analysis of trough concentrations from Study Days 11, 13 and 15 (p=0.2605 for Study Day 11 *vs.* 15, p=0.5276 for Study Day 13 *vs.* 15).
- When the dosing regimen of SQV was increased to 1200 mg BID in combination with LPV/r, steady-state is achieved after 5 days of dosing (by Day 20, p=0.4554 for Study Day 18 *vs.* 20).

Indinavir

- When dosed alone at 800 mg TID, IDV trough appeared to decrease from Day 3 to Day 5 ($p \leq 0.0001$); since IDV is not a metabolic inducer, it is expected that IDV concentrations will be at steady state after 3-4 days of dosing.
- IDV appears to approach steady state on Study Day 15, after 10 days of combination therapy with LPV/r based on analysis of trough concentrations from Study Days 11, 13 and 15 (p=0.0010 for Study Day 11 *vs.* 15 and p=0.3567 for Study Day 13 *vs.* 15).

Lopinavir and Ritonavir

- LPV appeared to approach steady state on Study Day 15, after 10 days of dosing in combination with both IDV 600 mg BID and SQV 800 mg BID based on analysis of trough concentrations from Study Days 11, 13 and 15 (for IDV and SQV, respectively, p <0.0001 and 0.097 for Study Day 11 *vs.* 15 and p=0.054 and 0.260 for Study Day 13 *vs.* 15).
- LPV concentrations remain steady on Days 18 and 20 during SQV 1200 mg BID (p=0.8406 for Study Day 15 *vs.* 20, p=0.9872 for Study Day 18 *vs.* 20).
- Similar results were observed for RTV.

DISCUSSION AND CONCLUSIONS

Saquinavir

- Dosed at 800 mg BID with LPV/r, steady-state SQV C_{max}, AUC, C_{min}, harmonic mean peak-to-trough $t_{1/2}$ were substantially increased relative to SQV 1200 mg TID alone; median IQ was increased from 0.3 to 5.2.
- SQV C_{min} and AUC were similar to or somewhat higher than those observed historically with SQV/r 400/400 mg BID.[2]
- There was no corresponding increase in SQV PK parameters when SQV was increased from 800 to 1200 mg, suggesting a plateau of concentrations at the 800 mg BID dosing regimen.

Indinavir

- Dosed at 600 mg BID with LPV/r, IDV C_{min} is increased by 3.5-fold and harmonic mean peak-to-trough $t_{1/2}$ was also increased relative to IDV 800 mg TID administered alone; IDV median IQ was increased from 4.3 to 11.
- Steady state IDV C_{max} was lower during coadministration.
- IDV C_{min} and AUC were similar to or slightly lower than those observed historically with IDV/r 800/100 mg BID.[3]

Lopinavir and Ritonavir

- From comparison to historical data, the pharmacokinetics of LPV and RTV appear to be minimally affected during saquinavir or indinavir coadministration; median IQ for LPV was >85 for all combination regimens.
- Increasing the dose of SQV from 800 to 1200 mg BID does not significantly affect lopinavir or ritonavir pharmacokinetics.

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