Assessment of Pharmacokinetic Variability for Lopinavir/ritonavir Tablet and Soft-Gel Capsule Formulations

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Lack of Food Effect on the Bioavailability of Lopinavir/ritonavir Tablet Formulation

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Background

- A novel melt-extrusion tablet formulation of lopinavir/ritonavir was developed that does not require refrigeration and reduces daily pill count compared to the soft gelatin capsule (SGC).
- Lopinavir/ritonavir SGC must be administered under fed conditions in order to maximize pharmacokinetic (PK) bioavailability of lopinavir.
- Relative to fasting, the bioavailability under moderate- and high-fat meal conditions increased by 56% and 96%, respectively, for the SGC formulation.
- After single-dose administration with moderate-fat meal, the tablet demonstrated modestly higher (approximately 18%) bioavailability relative to the SGC.
- The current analysis examines the variability of lopinavir and ritonavir PK parameters for each formulation.
- Also, the magnitude of food effect is formally assessed for a novel melt-extrusion tablet formulation of lopinavir/ritonavir.

Methods 1: Variability Assessment

- In a replicated crossover study, 46 healthy adults received single doses of lopinavir/ritonavir 400/100 mg as tablet (test, T) or SGC (reference, R) under moderate-fat meal conditions, separated by washout periods of at least 5 days.

Table 1. Demographics for Subjects Included in the Variability Assessment (N=46)

N (%)				Mean ± SD	
Female	14 (30%)	White	35 (76%)	Weight (kg)	75.5 ± 9.2
Male	32 (70%)	Black	7 (15%)	Age (years)	33.0 ± 10.1
		Hispanic	4 (9%)		

- Subjects were randomly assigned to one of the two sequences of drug administrations: TTR and RTT in three crossover periods.
- PK Blood samples were collected as follows: Pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30 and 36 hours following a single dose.
- Lopinavir (LPV) and ritonavir (RTV) PK variables were derived using non-compartmental methods including area under the plasma concentration time curve extrapolated to infinity (AUC_∞), maximum concentration (C_{max}) and concentration at 12 hours post-dose (C_{12}).
- A linear mixed effects model for replicated design was used to estimate the within- and between-subject variability of the log-transformed AUC_∞, C_{max} and C_{12} for each formulation.
- The total variance was calculated as the sum of the within- and between-subject variances.

Methods 2: Food Effect Assessment

- 106 healthy subjects in 2 randomized, open-label studies received single doses of lopinavir/ritonavir 400/100 mg SGC and tablet formulations in a crossover fashion under three different controlled meal conditions: fasting, moderate- and high-fat meals.

Table 2. Demographics for Subjects Included in the Food Effect Assessment (N=106)

N (%)				Mean ± SD	
Female	30 (28%)	White	76 (72%)	Weight (kg)	76.4 ± 9.2
Male	76 (72%)	Black	18 (17%)	Age (years)	34.5 ± 10.4
		Hispanic	12 (11%)		

- PK Blood samples were collected as follows: Pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30 and 36 hours following a single dose.
- PK parameters, including AUC until the last measurable value (AUC_t) as well as AUC_∞ and C_{max} of LPV and RTV, were estimated using standard non-compartmental methods.
- To assess the effect of food, the PK of the tablet under each of the meal conditions was compared to that of the SGC under the moderate-fat meal condition, which was chosen as the clinically relevant reference.
- LPV and RTV AUCs and C_{max} were logarithmically transformed for statistical analysis.
- Linear mixed effects modeling was performed and point estimate and 90% confidence interval (CI) provided.

Result 1: PK Variability for Tablets and SGC

Table 3. Overall Variability in LPV and RTV PK Parameters Was Reduced for the Tablet Compared to the SGC

PK Variable		Total Variance		Within-Subject Variance		Between-Subject Variance	
		Tablet	SGC	Tablet	SGC	Tablet	SGC
LPV	C_{max}	.213	.314	.014	.012	.199	.302
	AUC_∞	.217	.433	.018	.024	.199	.409
	C_{12}	.198	.461	.021	.025	.177	.436
RTV	C_{max}	.382	.579	.032	.043	.350	.536
	AUC_∞	.220	.507	.018	.040	.202	.467
	C_{12}	.243	.683	.029	.070	.214	.613

- The tablet formulation had considerably lower between-subject variability compared to the SGC formulation.
- The tablet formulation also had generally lower within-subject variability.
- The total variability (as the sum of within- and between-subject variances) was consistently lower for the tablet formulation.

Result 2: Food Effects for Tablets and SGC

Figure 1. LPV Concentrations vs. Time

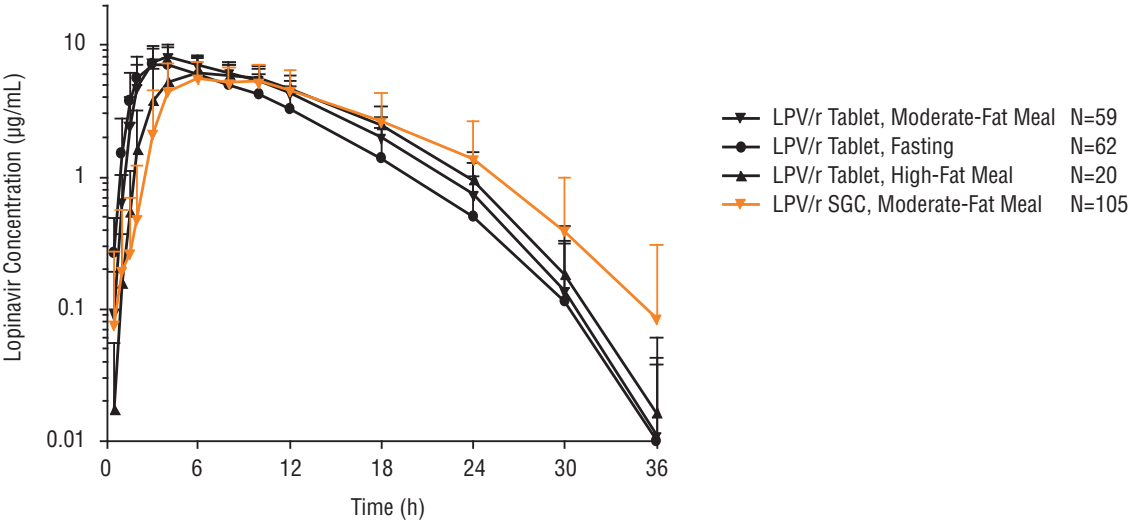

Figure 2. RTV Concentrations vs. Time

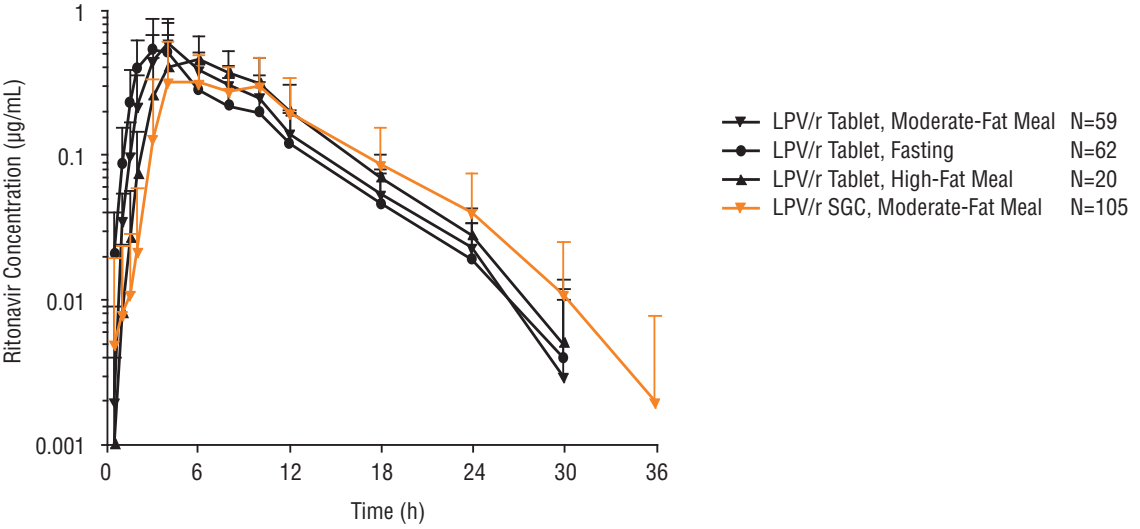

Table 4. LPV and RTV Bioavailability Under Various Meal Conditions for the Tablet Relative to the Reference SGC Formulations

Regimen Comparison	PK Variable	Point Estimate	90% CI
	LPV		
Tablet Fasting	C_{max} (µg/mL)	1.10	1.03 – 1.18
vs.	AUC_t (µg•h/mL)	1.00	0.93 – 1.08
SGC Moderate-Fat	AUC_∞ (µg•h/mL)	1.00	0.93 – 1.08
Tablet Mod-Fat	C_{max} (µg/mL)	1.24	1.19 – 1.29
vs.	AUC_t (µg•h/mL)	1.18	1.13 – 1.24
SGC Moderate-Fat	AUC_∞ (µg•h/mL)	1.18	1.13 – 1.24
Tablet High-Fat	C_{max} (µg/mL)	0.95	0.88 – 1.04
vs.	AUC_t (µg•h/mL)	1.01	0.92 – 1.11
SGC Moderate-Fat	AUC_∞ (µg•h/mL)	1.01	0.93 – 1.11
	RTV		
Tablet Fasting	C_{max} (µg/mL)	1.33	1.18 – 1.50
vs.	AUC_t (µg•h/mL)	1.10	1.01 – 1.20
SGC Moderate-Fat	AUC_∞ (µg•h/mL)	1.09	1.00 – 1.19
Tablet Mod-Fat	C_{max} (µg/mL)	1.35	1.26 – 1.44
vs.	AUC_t (µg•h/mL)	1.20	1.15 – 1.26
SGC Moderate-Fat	AUC_∞ (µg•h/mL)	1.19	1.14 – 1.25
Tablet High-Fat	C_{max} (µg/mL)	1.15	0.99 – 1.33
vs.	AUC_t (µg•h/mL)	1.15	1.05 – 1.26
SGC Moderate-Fat	AUC_∞ (µg•h/mL)	1.14	1.04 – 1.24

- The bioequivalence criteria were met with respect to LPV AUC_t and AUC_∞ when comparing the three meal conditions for the tablet relative to the SGC reference regimen because the 90% CIs were contained entirely within the 0.8–1.25 range.
- The bioequivalence criteria were also met for LPV C_{max} under fasting and high-fat meal conditions as compared to the SGC reference regimen.
- Similar trend was observed for RTV.

Conclusions

- The tablet formulation of lopinavir/ritonavir provides more consistent PK performance within and between subjects compared to the SGC.
- Fewer subjects are expected to experience extremely high or low lopinavir or ritonavir concentrations with the tablet compared to the SGC.
- The tablet formulation under different meal conditions resulted in lopinavir average concentrations and maximum exposures similar to the approved SGC reference regimen.
- The lopinavir/ritonavir tablet formulation may be taken without regard to food.

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