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New Tablet Formulation of Lopinavir/Ritonavir Is Bioequivalent to the Capsule at a Dose of 800/200 mg

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INTRODUCTION

Lopinavir (LPV) is an HIV protease inhibitor that is co-formulated with low-dose ritonavir (RTV), which enhances LPV pharmacokinetics (PK), and is marketed as Kaletra®.

- A dose of lopinavir/ritonavir (LPV/r) 800/200 mg once daily (QD) was recently approved in the United States for use in combination therapy for therapy-naïve HIV-infected adults.
- LPV/r is currently available as 133.3/33.3 mg soft gelatin capsule (SGC) or 80/20 mg/mL liquid formulations, requires refrigerated storage prior to dispensing and is recommended to be taken with food in order to maximize lopinavir exposure.
- A novel melt-extrusion technology was used to reduce pill count from 6 SGC per day to 4 tablets per day. In addition, this 200/50 mg tablet formulation of LPV/r does not require refrigeration.
- Bioavailability and safety data of a single dose of LPV/r 400/100 mg administered as the tablet to healthy adults was previously reported.[1]
  - At a dose of 400/100 mg, the tablet provided LPV and RTV exposures similar to the SGC under fed (moderate fat meal) conditions.
  - The tablet also provided more consistent LPV and RTV exposures across meal conditions (fasting, moderate fat meal, high fat meal), with reduced pharmacokinetic variability compared to the SGC.

SGC

Tablet

Melt Extrusion Technology (Meltrex™)

LPV/r is a low solubility/low permeability drug (Biopharmaceutics Classification System Class 4).

Historically, solid formulations of LPV/r showed poor bioavailability.

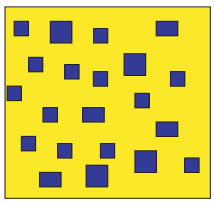
- Unformulated solid fails to provide bioavailability (<5%).
- Incorporation of surfactants, acids or other wetting agents with traditional technologies failed to provide adequate bioavailability for solid formulations.
- *In vitro* dissolution did not necessarily correlate with *in vivo* bioavailability.

Melt extrusion technology (Meltrex™) has overcome these challenges.

- Meltrex significantly improves the bioavailability of poorly soluble compounds like LPV/r by dissolving drug in polymer in a solvent-free environment. The drug remains in a state of molecular dispersion as the polymer hardens to form extruded material.
- This extruded material can be further processed into conventional tablets.
- Excipients used for the tablet are different than those in the SGC. Specifically, the tablet does not contain certain excipients (such as oleic acid, propylene glycol, sorbitol and castor oil) found in the SGC, which may contribute to gastrointestinal side effects.

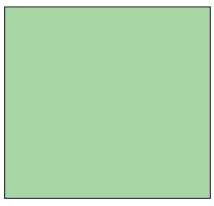
Meltrex™: Amorphous Solid Dispersion Formulation

Traditional Tablet



Drug crystals
(50–150 µm)
mixed with excipients

Solid Dispersion



Drug dissolved in a
hydrophilic polymer
(glassy solution)

PURPOSE

To develop a LPV/r tablet formulation to reduce pill count, allow for room temperature storage and maintain bioavailability similar to the SGC formulation under fed conditions at a dose of 800/200 mg (4 tablets).

STUDY METHODS

- Healthy subjects (N=15) with Body Mass Index of 18 to 27 kg/m^2 were enrolled into this Phase 1, open-label, randomized, cross-over study (Table 1).
- Single doses of LPV/r 800/200 mg as tablet or SGC formulation were separated by at least 5 days.
- LPV/r was administered after a moderate-fat breakfast (492 kCal, 23% from fat), as the SGC is recommended to be taken with food.

Pharmacokinetic Analysis

Blood samples were collected for LPV and RTV assay as follows:

- Pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours following a single dose

Drug concentrations were measured by validated LC/MS/MS methods:

- LPV limit of quantitation (LOQ) = 20 ng/mL
- RTV LOQ = 11 ng/mL

LPV and RTV PK parameters were calculated with standard non-compartmental analysis using WINNONLIN v. 4.1 software (Pharsight Corp., Mountain View, CA) to estimate the maximum observed concentration (C_{max}), concentration 24 hours post-dosing (C_{24}), area under the plasma concentration time curve (AUC) to the last measured concentration (AUC_t) and to infinity (AUC_∞), and terminal phase half-life ($t_{1/2}$).

Statistical Analysis

The bioavailability of the tablet relative to the SGC was assessed by a two one-sided tests procedure via 90% confidence intervals obtained from the analysis of the natural logarithms of C_{max}, AUC_t and AUC_∞ within the framework of the ANOVA model using the SAS system v. 6.12 software (SAS Institute, Cary, NC).

Safety Analysis

Safety and tolerability were assessed throughout the study based on reported adverse events, vital signs, electrocardiograms and clinical laboratory measurements.

Table 1. Demographics of Subjects Receiving 800/200 mg Dose

	N=15
Subjects	Healthy Adults
Sex	12 Males (80%) 3 Females (20%)
Race/Ethnicity	12 White (80%) 1 Black (7%) 2 Hispanic (13%)
Age (years)*	36 ± 12 (19–53)
Weight (kg)*	77 ± 10 (58–96)
Height (cm)*	175 ± 6.2 (158–183)

* Mean ± SD (range)

RESULTS

The concentration-time profiles for LPV and RTV were similar following single dose administration of 800/200 mg as the tablet or SGC (Figures 1 and 2).

Figure 1. LPV Concentration-Time Profile

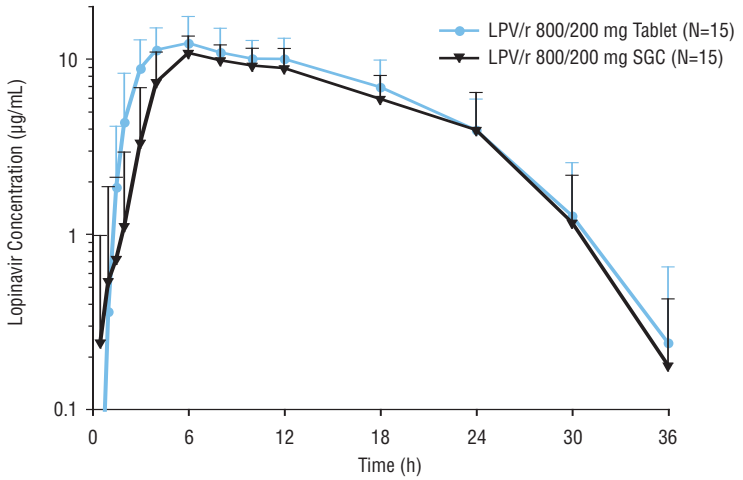
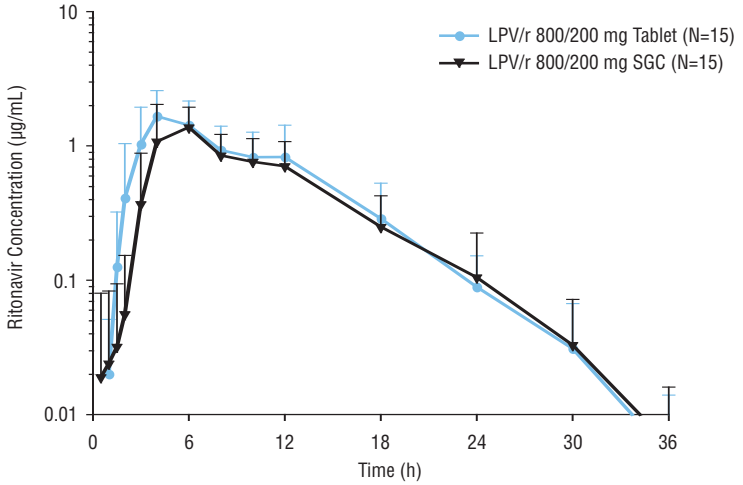


Figure 2. RTV Concentration-Time Profile



The pharmacokinetic parameters following a single dose of LPV/r 800/200 mg as the tablet or SGC are shown in Table 2.

Table 2. Pharmacokinetic Parameters of Lopinavir and Ritonavir Following a Single 800/200 mg Dose

Formulation	Tablet	SGC	
Pharmacokinetic Parameters (units)		**N=15**	**N=15**
		Lopinavir	
T_{max}	(h)	5.5 ± 2.3	6.1 ± 2.1
C_{max}	(µg/mL)	13.74 ± 4.92*	11.72 ± 2.43
C_{24}	(µg/mL)	3.98 ± 2.01	4.00 ± 2.54
AUC_{∞}	(µg•h/mL)	214.2 ± 69.6*	181.4 ± 51.5
$t_{1/2}$	(h)	2.49 ± 0.68	2.36 ± 0.49
		Ritonavir	
T_{max}	(h)	4.8 ± 1.0*	5.5 ± 0.9
C_{max}	(µg/mL)	1.96 ± 0.86*	1.72 ± 0.74
C_{24}	(µg/mL)	0.09 ± 0.06	0.11 ± 0.12
AUC_{∞}	(µg•h/mL)	16.1 ± 7.6*	13.3 ± 5.6
$t_{1/2}$	(h)	3.63 ± 0.55	3.79 ± 0.60

Mean ± Standard Deviation
800/200 mg administered after a moderate-fat meal.
* Statistically significantly different from SGC (ANOVA, $p<0.05$).

Following a single dose of LPV/r 800/200 mg, the tablet is bioequivalent to the SGC with respect to LPV C_{max} and AUC under moderate-fat meal conditions (Table 3).

Table 3. Tablet Provides Similar Exposure to SGC Under Moderate-Fat Meal Conditions

	Central Values*		Relative Bioavailability	
Parameter	**Tablet**	**SGC**	**Point Estimate†**	**90% Confidence Interval**
		Lopinavir		
C_{max}	13.1 µg/mL	11.5 µg/mL	1.140	1.044 – 1.244
AUC_t	202.2 µg•h/mL	173.1 µg•h/mL	1.168	1.121 – 1.217
AUC_∞	203.7 µg•h/mL	173.9 µg•h/mL	1.172	1.126 – 1.219
		Ritonavir		
C_{max}	1.8 µg/mL	1.6 µg/mL	1.133	1.024 – 1.253
AUC_t	14.0 µg•h/mL	11.9 µg•h/mL	1.174	1.090 – 1.264
AUC_∞	14.1 µg•h/mL	12.0 µg•h/mL	1.173	1.091 – 1.260

* Antilogarithm of the least squares means for logarithms.
† Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
Note: Tablets and SGCs administered as a single 800/200 mg dose.

SAFETY PROFILE

15 healthy adults received the tablet formulation at a dose of 800/200 mg.

All adverse events (AE) were mild in severity.

Table 4. Adverse Events with 800/200 mg Dose

	Tablet	SGC
Any AE	27%	40%
Loose Stool or Diarrhea	13%	27%
Headache	13%	7%
Abdominal Pain	7%	7%
Taste Perversion	0%	7%

CONCLUSIONS

A single dose of 800/200 mg LPV/r administered as the tablet was bioequivalent, with respect to LPV, to 800/200 mg LPV/r as the SGC. The 90% confidence interval for LPV AUC and C_{max} of the tablet compared to the SGC was within 0.80–1.25.

The new LPV/r tablet formulation exhibited slightly higher bioavailability, approximately 17%, for both LPV and RTV following a single dose of 800/200 mg compared to the SGC.

The tablet formulation was well tolerated and tended to result in a lower incidence of gastrointestinal side effects compared to the SGC in healthy adults receiving single 800/200 mg doses.

ACKNOWLEDGMENTS

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Soliqs Formulation Development Team

REFERENCE

1. Awni W, Chiu YL, Zhu T, et al. Significantly reduced food effect and pharmacokinetic variability with a novel lopinavir/ritonavir tablet formulation. Poster presented at: Third International AIDS Society Conference on HIV Pathogenesis and Treatment; July 24–27, 2005; Rio de Janeiro, Brazil. WeOa0206.