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Significantly Reduced Food Effect and Pharmacokinetic Variability with a Novel Lopinavir/ritonavir Tablet Formulation

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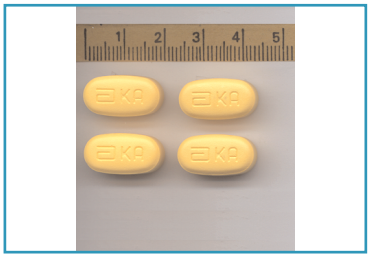
INTRODUCTION

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

- LPV/r is currently available as 133.3/33.3 mg soft gelatin capsule (SGC) or 80/20 mg/mL liquid formulation, requires refrigerated storage prior to dispensing, and is recommended to be taken with food in order to optimize 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.

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.

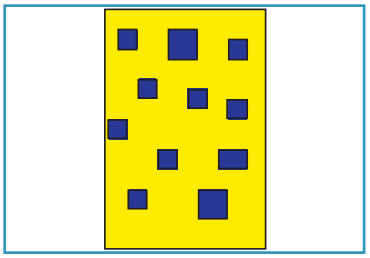
- Unformulated solid fails to provide bioavailability (<5%).
- Incorporation of surfactants, acids or other wetting agents with traditional technologies failed to provide adequate bioavailability for solid formulations.
- *In vitro* dissolution did not necessarily correlate with *in vivo* bioavailability.

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.
- This extruded material can be shaped as tablets, granules, pellets, sheets, sticks, or powder which can be further processed into conventional tablets.

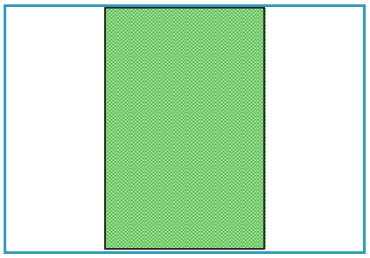
Meltrex™: Amorphous Solid Dispersion Formulation

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.

STUDY METHODS

The tablet formulation was evaluated by one pilot single- and multiple-dose study and two studies using production scale lots.

Single-dose PK, relative bioavailability and safety of the 400/100 mg dose are reported here.

- Studies assessed the relative bioavailability of a LPV/r 400/100 mg tablet dose compared to SGC under moderate fat meal conditions since the SGC is recommended to be taken with food.
- In addition, the relative bioavailability of the LPV/r 400/100 mg dose as the tablet was assessed under various meal conditions.

Study Designs

- Healthy subjects (N=141 single dose, of whom 23 also received multiple doses, Table 1) were enrolled into these Phase 1, open-label, randomized, cross-over studies if they met the following criteria:
  - General good health
  - No concomitant medication
  - Body Mass Index 18 to 27 kg/m^2
- Subjects were equally randomized to each regimen sequence in each study.
- Single doses were separated by at least 5 days. LPV/r was adminisistered under fasting conditions, after a moderate-fat breakfast (500-600 kCal, 20-30% from fat), or after a high-fat breakfast (~1000 kCal, 50% from fat).

Pharmacokinetic Analysis

Blood samples were collected for LPV and RTV assays 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

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

- LPV limit of quantitation (LOQ) = 5 ng/mL
- RTV LOQ = 1 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}), 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 test 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 Single Doses of Tablet Formulation

	N=138†
Subjects	Healthy Adults
Sex	105 Males (76%) 33 Females (24%)
Race/Ethnicity	99 White (72%) 23 Black (17%) 16 Hispanic (12%)
Age (years)*	35 ± 11 (19–55)
Weight (kg)*	77 ± 10 (55–101)
Height (cm)*	176 ± 9 (147–192)

* Mean ± SD (range)
† 3 Subjects discontinued for personal reasons prior to receiving tablet formulation

RESULTS

Following a single dose of LPV/r 400/100 mg, the tablet provides similar LPV and RTV exposures to SGC under moderate fat meal conditions (Figures 1 and 2).

Figure 1. LPV Concentration Time Profile

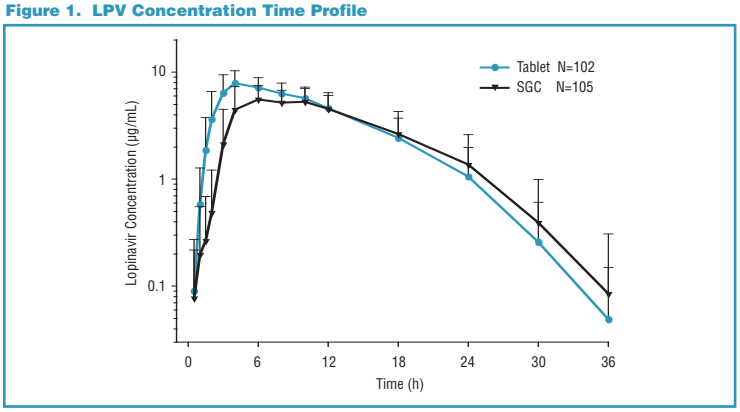
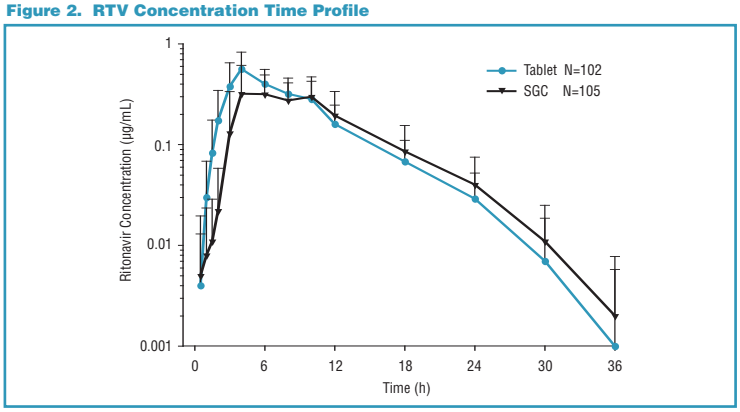


Figure 2. RTV Concentration Time Profile



RESULTS (CONTINUED)

The tablet met bioequivalence criteria with respect to LPV and RTV AUC relative to the SGC at a dose of 400/100 mg under the reference moderate-fat meal conditions (Table 2).

Table 2. Tablet Provides Similar Exposure to SGC Under Moderate-Fat Meal Conditions

Pharmacokinetic Parameter	Central Values*		Relative Bioavailability	
	Tablet	SGC	Point Estimate†	90% Confidence Interval
Lopinavir				
C_{max}	8.0 µg/mL	6.5 µg/mL	1.235	1.188 – 1.285
AUC_t	95.8 µg•hr/mL	80.9 µg•hr/mL	1.184	1.131 – 1.239
AUC_∞	96.2 µg•hr/mL	81.5 µg•hr/mL	1.181	1.129 – 1.236
Ritonavir				
C_{max}	0.6 µg/mL	0.4 µg/mL	1.349	1.263 – 1.441
AUC_t	4.3 µg•hr/mL	3.6 µg•hr/mL	1.202	1.146 – 1.261
AUC_∞	4.4 µg•hr/mL	3.7 µg•hr/mL	1.193	1.139 – 1.249

* 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 400/100 mg dose.

The tablet has significantly reduced food effect compared to the SGC (Figures 3, 4, 5, and 6, Table 3).

Figure 3. Tablet Lacks Significant Food Effect—LPV

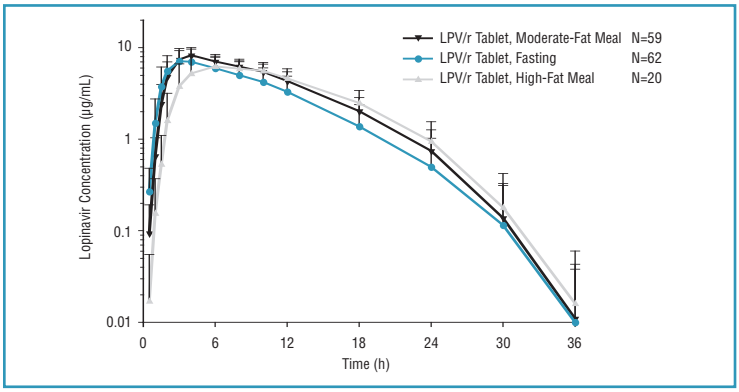


Figure 4. Tablet Lacks Significant Food Effect—RTV

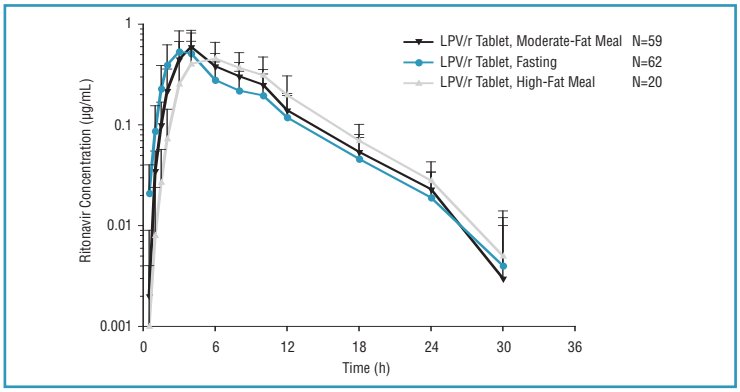


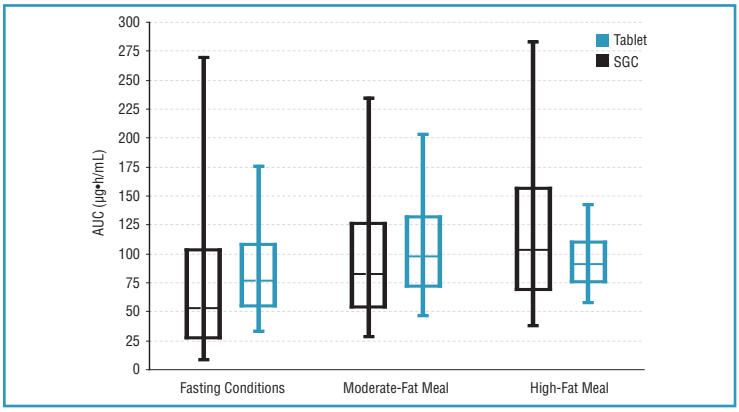
Table 3. Tablet Provides Similar Exposure Under Fasting and Non-Fasting Conditions

Regimens	PK Parameter	Central Values*		Relative Bioavailability	
		Test	Reference	Point Estimate†	90% Confidence Interval
Lopinavir					
Moderate-Fat *vs.* Fasting	C_{max}	8.2 µg/mL	7.0 µg/mL	1.176	1.111 – 1.244
	AUC_∞	97.1 µg•hr/mL	76.5 µg•hr/mL	1.269	1.191 – 1.352
High-Fat *vs.* Fasting	C_{max}	6.9 µg/mL	7.0 µg/mL	0.993	0.877 – 1.124
	AUC_∞	87.1 µg•hr/mL	73.3 µg•hr/mL	1.189	1.029 – 1.373
Ritonavir					
Moderate-Fat *vs.* Fasting	C_{max}	0.5 µg/mL	0.5 µg/mL	1.049	0.943 – 1.167
	AUC_∞	4.2 µg•hr/mL	3.7 µg•hr/mL	1.149	1.063 – 1.241
High-Fat *vs.* Fasting	C_{max}	0.5 µg/mL	0.5 µg/mL	1.103	0.920 – 1.323
	AUC_∞	4.4 µg•hr/mL	3.6 µg•hr/mL	1.239	1.068 – 1.436

* Antilogarithm of the least squares means for logarithms.
† Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.
Note: Tablets administered as a single 400/100 mg dose.

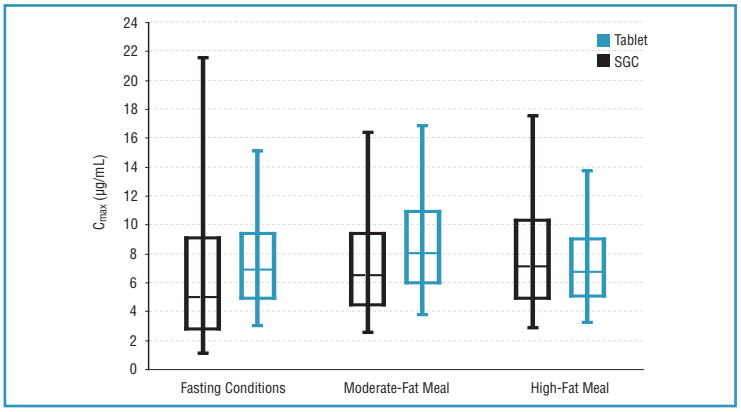
The tablet provides consistent exposure to LPV and RTV regardless of meal conditions with further reduced pharmacokinetic variability compared to the SGC under any meal condition (Figures 5 and 6).

Figure 5. LPV AUC Under Various Meal Conditions



Shown are the lower and upper quartiles (box), median (horizontal line in box), and 5th and 95th percentiles (whiskers).

Figure 6. LPV C_{max} Under Various Meal Conditions



Shown are the lower and upper quartiles (box), median (horizontal line in box), and 5th and 95th percentiles (whiskers).

SAFETY PROFILE

138 healthy adults received the tablet formulation.

The vast majority of adverse events were mild in severity. Moderate or severe adverse events are shown in Table 4. The tablet formulation was safe and well tolerated. No subject discontinued due to a drug-related adverse event.

Table 4. Frequency of Moderate or Severe Adverse Events After Single Dose Administration (400/100 mg)

Adverse Event	Tablet	SGC
Diarrhea	0.3%	1.1%
Any Moderate or Severe Adverse Event	0.7%	1.1%

Multiple-dose administration of the tablet was similarly safe and well tolerated.

CONCLUSIONS

Benefits of the tablet formulation include reduced pill count, room temperature storage, lack of significant food effect and lower variability of LPV levels compared to the SGC.

The 90% confidence interval for LPV AUC of the tablet to the SGC was within 0.80–1.25 and the C_{max} extended slightly above 1.25 to 1.285.

The tablet formulation shows an ~18% increase in LPV bioavailability relative to the SGC.

- Despite this modest increase in average bioavailability the tablet is expected to produce narrower ranges of concentrations than the SGC with fewer patients likely to be exposed to high or low LPV concentrations.
- The tablet is expected to provide more consistent LPV and RTV levels day to day as meal conditions vary.

The tablet formulation was safe and well tolerated and appeared to result in lower incidence of GI effects compared to the SGC in healthy subjects receiving single doses.

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