

# The Pharmacokinetic Interaction Between the CCR5 Antagonist 873140 and Lopinavir/Ritonavir in Healthy Subjects

## Introduction

- 873140 is a potent and specific chemokine receptor 5 (CCR5) antagonist that inhibits CCR5-tropic HIV-1 replication in vitro at subnanomolar concentrations. In vitro human liver microsomal studies have shown that 873140 is metabolized by CYP450 3A4.
- KALETRA (lopinavir/ritonavir; LPV/RTV) is a co-formulation of two HIV protease inhibitors and is a common component of antiretroviral therapy. Ritonavir and lopinavir are inhibitors of the drug metabolizing enzyme, CYP450 3A4.
- This study explored the potential for a drug-drug interaction between 873140 and LPV/RTV. The specific objectives were as follows:

### Primary:

- To compare the steady-state plasma 873140 PK with and without LPV/RTV
- To assess the safety and tolerability of single and repeat dose co-administration

### Secondary:

- To compare steady-state plasma LPV and RTV PK with and without 873140
- To compare single dose plasma 873140 PK with and without RTV and describe RTV single dose PK

## Methods

The study was a Phase 1, single center, inpatient, open label study in healthy male and female adult subjects ( $\geq 18$  and  $\leq 55$  years of age). The study was conducted in two parts. Part 1 was a single dose study of low dose 873140 and RTV to evaluate the potential magnitude of inhibition and choose an 873140 dose for Part 2. Part 2 was a repeat-dose study of 873140 and LPV/RTV. All doses were administered with a 30% fat meal.

### Study Design — Part 1 (Single Dose; N=8):

Part 1	Day 1	Day 2	Day 3	Days 4 and 5
Cohort 1	873140 50mg	Washout	873140 50mg + RTV 100mg	PK & Safety

Clinical laboratory tests were collected on Days 1-5 and at the follow-up visit. Serial PK blood samples were collected on Days 1 and 3 at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 (Day 3 only) and 48h (Day 3 only) post-dose.

### Study Design — Part 2 (Repeat Dose; N=25):

Part 2	Period 1 Study days 1-7	Period 2 Study days 8-21	Period 3 Study days 22-28
Cohort 2	873140 400mg q12h (Treatment A)	LPV 400mg/RTV 100 mg q12h (Treatment B)	LPV 400mg/RTV 100 mg + 873140 400mg q12h (Treatment C)

Clinical laboratory tests were conducted on Days 1, 7, 8, 12, 17, 21, 22, 28, 29 and at follow-up 7-10 days after the last dose. Serial blood samples for PK were obtained at 0, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12h post-morning dose on Day 7 Period 1, Day 14 Period 2, and Days 1 and 7 of Period 3. Additional samples were obtained prior to the morning dose on Days 3, 4, 5, 6 of Period 3 and at 16 and 24h post-dose on Day 7 Period 3.

### Pharmacokinetics

Plasma samples were analyzed for 873140 and RTV by a validated LC/MS/MS method with a calibration range of 0.5 to 500ng/mL and 1 to 1000ng/mL, respectively. Plasma LPV concentrations were measured by a separate validated LC/MS/MS assay with a lower limit of quantitation of 20ng/mL. Plasma PK parameters for 873140, LPV, and RTV were estimated by standard noncompartmental methods using WinNonlin Professional v4.1 (Pharsight, Mountain View, CA).

### Statistical Comparisons

Comparisons of interest were assessed by ANOVA using SAS (Cary, NC) PROC MIXED to construct the ratio of treatments of test versus reference.

## Results

Table 1. Summary of Demographic Data

	Part 1 (Single dose)	Part 2 (Repeat dose)
N (Started/Completed)	8/8	24/22
Age (yrs)	39.4 $\pm$ 10.7	36.2 $\pm$ 11.4
Sex (M/F)	3/5	16/8
Race/Ethnicity	4 W, 4 H	15 H, 8 W, 1 B
Weight (kg)	68.8 $\pm$ 11.7	72.6 $\pm$ 9.6
Body Mass Index	25.0 $\pm$ 2.6	25.7 $\pm$ 2.5

Data reported as mean  $\pm$  SD  
Abbreviations: W, Caucasian; H, Hispanic; B, African-American

### Pharmacokinetics — Part 1 (Single Dose)

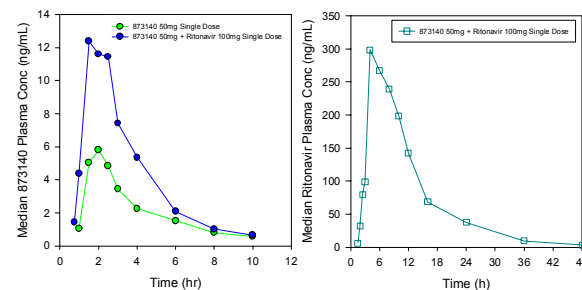
Single dose co-administration of RTV 100mg with a low dose of 873140 significantly increased the 873140 AUC(0- $\infty$ ) and C<sub>max</sub> by 2.2-fold (Table 2; Figure 1). Based on this modest change in exposure and consideration of toxicological and human safety coverage, an 873140 dose regimen of 400mg q12h was selected for Part 2.

Table 2. Plasma 873140 PK Parameters and Treatment Comparisons—Part 1 Single Dose

873140 PK Parameter <sup>a</sup>	Treatment <sup>a</sup>		Treatment Comparison <sup>c</sup>
	873140 (A) n=8	873140 + RTV (B) n=8	
AUC(0- $\infty$ ), ng.h/mL	20.6 (16.6, 25.4)	43.7 (35.8, 53.3)	2.13 (1.88, 2.41)
C <sub>max</sub> , ng/mL	6.59 (5.09, 8.54)	14.7 (12.2, 17.7)	2.22 (1.72, 2.87)
T <sub>max</sub> , h	1.75 (1.0-3.0)	2.01 (1.0-2.5)	NC
T <sub>1/2</sub> , h	3.03 (2.48, 3.71)	2.10 (1.79, 2.45)	NC

<sup>a</sup>Treatment A: 873140 50mg single dose; Treatment B: 873140 50mg single dose + RTV 100mg single dose  
<sup>b</sup>Geometric mean values (95% confidence interval) presented for all parameters except T<sub>max</sub> (median, range)  
<sup>c</sup>Geometric least squares means ratio (90% confidence interval)  
NC: Not calculated

Figure 1. Plasma Concentration-Time Profiles of 873140 and RTV Following Single Doses



### Pharmacokinetics — Part 2

Repeated co-administration of LPV/RTV with 873140 resulted in a significant increase in 873140 plasma AUC(0- $\tau$ ), C<sub>max</sub>, and C<sub>t</sub> (Table 3; Figure 2) with minimal effects on T<sub>1/2</sub>.

Repeated co-administration of LPV/RTV with 873140 resulted in a modest 1.3-fold increase in RTV AUC(0- $\tau$ ) and C<sub>max</sub>, but had no effect on LPV AUC and C<sub>max</sub> (Tables 4 and 5, Figure 2).

Figure 2. Plasma Concentration-Time Profiles of 873140, LPV, and RTV During Repeat Dosing

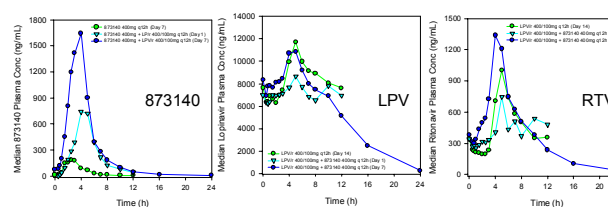


Table 3. Summary of 873140 PK Parameters and Treatment Comparisons—Part 2 Repeat Dose

873140 PK Parameter <sup>a</sup>	Treatment <sup>a</sup>			Treatment Comparison <sup>c</sup>
	873140 (A) Day 7, n=22	873140 + LPV/RTV (C) Day 7, n=22	873140 + LPV/RTV (B) Day 7, n=22	
AUC(0- $\tau$ ), ng.h/mL	808 (645, 1013)	307 (3079, 4227)	6229 (4832, 8031)	7.71 (6.39, 9.29)
C <sub>max</sub> , ng/mL	300 (221, 408)	800 (635, 1009)	1864 (1437, 2418)	6.21 (4.77, 8.10)
T <sub>max</sub> , h	2.5 (1.5-5.0)	5.0 (2.0-5.02)	4.0 (1.5-5.02)	NC
C <sub>t</sub> , ng/mL	6.47 (5.23, 8.01)	NC	45.9 (33.4, 62.9)	7.09 (5.56, 9.04)

<sup>a</sup>Treatment A: 873140 400mg q12h for 7 days; Treatment B: Lopinavir/ritonavir 400/100mg q12h for 14 days; C: 873140 400mg + lopinavir/ritonavir 400/100mg q12h for 7 days  
<sup>b</sup>Geometric mean values (95% confidence interval) presented for all parameters except T<sub>max</sub> (median, range)  
<sup>c</sup>Geometric least squares means ratio (90% confidence interval)

Table 4. Summary of Lopinavir PK Parameters and Treatment Comparisons—Part 2 Repeat Dose

LPV PK Parameter <sup>a</sup>	Treatment <sup>a</sup>		Treatment Comparison <sup>c</sup>
	LPV/RTV (B) Day 14, n=22	LPV/RTV + 873140 (C) Day 7, n=22	
AUC(0- $\tau$ ), ng.h/mL	98114 (87560, 109940)	95775 (83820, 108979)	0.97 (0.88, 1.08)
C <sub>max</sub> , ng/mL	12198 (10830, 13739)	11773 (10325, 13424)	0.97 (0.86, 1.08)
T <sub>max</sub> , h	5.0 (3.05-11.97)	4.5 (0-8.0)	NC
C <sub>t</sub> , ng/mL	6927 (5783, 8298)	5226 (4267, 6401)	0.75 (0.64, 0.89)

<sup>a</sup>Treatment A: 873140 400mg q12h for 7 days; Treatment B: Lopinavir/ritonavir 400/100mg q12h for 14 days; C: 873140 400mg + lopinavir/ritonavir 400/100mg q12h for 7 days  
<sup>b</sup>Geometric mean values (95% confidence interval) presented for all parameters except T<sub>max</sub> (median, range)  
<sup>c</sup>Geometric least squares means ratio (90% confidence interval)

Table 5. Summary of Ritonavir PK Parameters and Treatment Comparisons—Part 2 Repeat Dose

RTV PK Parameter <sup>a</sup>	Treatment <sup>a</sup>		Treatment Comparison <sup>c</sup>
	LPV/RTV (B) Day 14, n=22	LPV/RTV + 873140 (C) Day 7, n=22	
AUC(0- $\tau$ ), ng.h/mL	5875 (5066, 6815)	7510 (6318, 8926)	1.28 (1.11, 1.47)
C <sub>max</sub> , ng/mL	1090 (916, 1298)	1440 (1138, 1824)	1.32 (1.09, 1.61)
T <sub>max</sub> , h	5.0 (1.5-7.0)	4.5 (0-5.02)	NC
C <sub>t</sub> , ng/mL	332 (259, 425)	220 (174, 278)	0.66 (0.53, 0.84)

<sup>a</sup>Treatment A: 873140 400mg q12h for 7 days; Treatment B: Lopinavir/ritonavir 400/100mg q12h for 14 days; C: 873140 400mg + lopinavir/ritonavir 400/100mg q12h for 7 days  
<sup>b</sup>Geometric mean values (95% confidence interval) presented for all parameters except T<sub>max</sub> (median, range)  
<sup>c</sup>Geometric least squares means ratio (90% confidence interval)

Table 6. Summary of most frequently reported drug-related clinical adverse events (>10% subjects)—Part 2 Repeat Dose

	873140 N=24	KALETRA N=23	873140 + KALETRA N=22
Any Event	12/24 (50%)	11/23 (48%)	11/22 (50%)
Gastrointestinal:			
Loose stools	11/24 (46%)	4/23 (17%)	5/23 (23%)
Nausea	5/24 (21%)	4/23 (17%)	7/22 (32%)
Abdominal pain	1/24 (4%)	4/23 (17%)	1/22 (5%)
Vomiting	0/24 (0%)	0/23 (0%)	3/22 (14%)
Diarrhea	1/24 (4%)	4/23 (17%)	0/22 (0%)
Metabolism and Nutrition:			
Anorexia	0/24 (0%)	0/23 (0%)	4/22 (18%)

All AEs classified as Grade 1

## Adverse Events

All AEs were classified as Grade 1 with no serious AEs reported and no drug-related discontinuations. The most common AEs were gastrointestinal and are presented by symptom and frequency in Table 6. Gastrointestinal adverse events generally occurred on Day 1 and resolved within 1-3 days while subjects continued dosing.

## Discussion

- Co-administration of single dose of 873140 (50mg) with ritonavir (100mg) resulted in a 2.2-fold increase in 873140 plasma AUC(0- $\infty$ ) and C<sub>max</sub>
- Repeated co-administration of 873140 (400mg q12h) and lopinavir/ritonavir (400/100mg q12h) resulted in significant 7.7-, 6.2-, and 7.1-fold increases in the 873140 AUC(0- $\tau$ ), C<sub>max</sub>, and C<sub>t</sub>, respectively.
- The results were consistent with in vitro metabolism data which showed that 873140 was a CYP3A4 substrate and that RTV and LPV are CYP3A4 inhibitors.
- Repeat dose co-administration of 873140 (400mg q12h) and lopinavir/ritonavir (400/100mg q12h) resulted in a modest 1.3-fold increase in the ritonavir AUC(0- $\tau$ ) and C<sub>max</sub>, but had no effect on the LPV AUC(0- $\tau$ ) and C<sub>max</sub>. The RTV and LPV C<sub>t</sub> values were reduced 34% and 25% when co-administered with 873140. The LPV C<sub>t</sub> values are within the reported therapeutic range.
- Repeat dose co-administration of 873140 and lopinavir/ritonavir was well-tolerated. All AEs were reported as Grade 1 despite the high concentrations of 873140 achieved with concomitant lopinavir/ritonavir suggesting a large therapeutic window for safety with concomitant CYP3A4 inhibitors.

## Conclusions

- The significant increase in 873140 PK parameters in the presence of LPV/RTV warrants 873140 dose reductions when co-administered with LPV/RTV.
- The modest reduction in RTV and LPV C<sub>t</sub> is not expected to be clinically significant.
- The combination of 873140 and lopinavir/ritonavir demonstrated an acceptable safety profile enabling co-administration in clinical trials.