Comparison of Lopinavir and Ritonavir Tablet and Soft Gelatin Capsule (SGC) Pharmacokinetics in Antiretroviral-Naïve HIV-1 Infected Subjects

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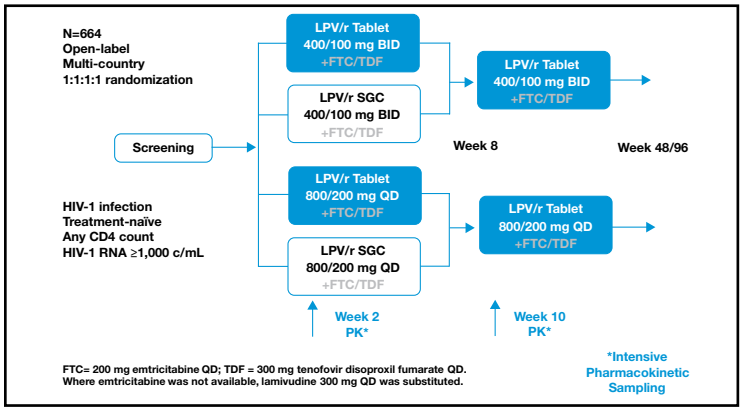
Poster P37

Introduction and Background

- Highly active antiretroviral therapy (HAART) consisting of three or more antiretroviral agents has been shown to reduce HIV type 1 (HIV-1) replication below the lower limits of detection, increase CD4 T-cell counts, decrease morbidity, increase life expectancy and improve quality of life for HIV-1 infected subjects.[1,2]
- Regimens with low pill count and with lower frequency of administration are of interest to clinicians and patients as they may increase convenience and promote adherence.
- Abbott developed a tablet formulation of lopinavir/ritonavir (LPV/r) that reduced the total pill count of the 800/200 mg LPV/r daily dose from 6 capsules with the SGC to 4 tablets and does not require refrigeration.
  - The tablet was approximately 18% more bioavailable than the SGC following single dose administration in healthy volunteers.
  - Recently published data in HIV-1-infected subjects demonstrated that the tablet and SGC formulations displayed similar rates of adverse events and laboratory abnormalities, and that the tablet formulation dosed once daily (QD) or twice daily (BID) had similar safety and antiviral activity through 48 weeks of therapy.[3]
- This analysis compares the pharmacokinetics of the LPV/r tablet to the SGC when dosed BID or QD with nucleoside reverse transcriptase inhibitors in HIV-1 infected subjects participating in Study M05-730.

Figure 1. Study M05-730 Design



Primary Efficacy Endpoints through Week 48

- 77% of QD- and 76% of BID-treated subjects achieved HIV-1 RNA <50 copies/mL at Week 48 (ITT NC=F)
- Difference in response rates (QD *minus* BID) and 95% confidence interval (CI): 1% (–5% to 8%)
  - Confirming the non-inferiority of the QD regimen to the BID regimen, as the lower bound of the CI was within the pre-specified margin of –12%
  - On-treatment data validate this finding
- Sensitivity analysis adjusting for the baseline imbalance in HIV-1 RNA level consistent with the primary analysis
  - Estimated difference (95% CI) in response rates: 1% (–6% to 7%)

Secondary Efficacy Endpoints through Week 48

- Similar proportion of QD- and BID-treated subjects achieved HIV-1 RNA <50 copies/mL at Week 48 within subgroups defined by:
  - Baseline HIV-1 RNA (<100,000 copies/mL or ≥100,000 copies/mL)
  - Baseline CD4+ T-cell count (<50 cells, 50–200 cells and ≥200 cells/mm^3)
- Similar mean increases from baseline in CD4+ T-cell count in the QD and BID groups: 186 and 197 cells/mm^3, respectively (p=0.350) at Week 48

Safety Analysis through Week 48

- Rate of study drug-related diarrhea of moderate or greater severity was similar between groups
  - QD 17%, BID 15%, p=0.671
- Rates of other events of interest and Grade 3+ laboratory abnormalities were also similar in the two treatment groups
- While mean increases were observed in both groups in all lipid parameters, the mean LDL-C:HDL-C ratio decreased substantially in both groups

Objective

- Compare the relative bioavailability of the LPV/r tablet formulation with the SGC formulation in HIV-infected, treatment-naïve subjects.

Study Methods and Design

- Antiretroviral-naïve HIV-1 infected adults (N=664) were enrolled into this Phase 3, multiple-dose, open-label, multi-center, multi-country study if they met the following criteria:
  - Naïve to antiretroviral treatment
  - Not treated for an active acquired immune deficiency syndrome (AIDS)-defining opportunistic infection within 45 days of initiating study drug
  - A plasma HIV-1 RNA level of greater than or equal to 1,000 copies/mL at screening and, in the investigator's opinion, required antiretroviral therapy
  - No drugs that were contraindicated or had significant pharmacokinetic interactions with study drugs during the course of the study

Pharmacokinetic Analysis

- At selected sites, up to a total of 20 subjects randomized to each of the QD treatment groups (tablet QD and SGC QD) and BID treatment groups (tablet BID and SGC BID) were planned for the 24-hour (QD) and 12-hour (BID) pharmacokinetic evaluation of lopinavir (LPV) and ritonavir (RTV).
- 69 subjects were included in the PK analyses at Weeks 2 and 10.
- Blood samples were collected for LPV and RTV assay at pre-dose (0 hour) and at 2, 4, 6, 8 and 12 hours after dosing at Weeks 2 and 10 for BID treatment groups, and at pre-dose (0 hour) and at 2, 4, 6, 8, 12 and 24 hours after dosing at Weeks 2 and 10 for QD treatment groups.
- Drug concentrations for LPV and RTV were measured by validated LC/MS/MS methods:
  - LPV lower limit of quantitation (LLOQ) = 5.00 ng/mL
  - RTV LLOQ = 1.00 ng/mL
- LPV and RTV PK parameters were calculated with standard non-compartmental analysis using WinNonlin v. 5.0.1 software (Pharsight Corp., Mountain View, CA) to estimate the minimum observed concentration (C_{min}), concentration prior to morning dose (C_{trough}), maximum observed concentration (C_{max}), time to the maximum observed concentration (T_{max}), area under the plasma concentration time curve from time 0 to 12 hours (AUC_{12}), and AUC from time 0 to 24 hours (AUC_{24}).

Results

Table 1. Demographics of Subjects Included in PK Analyses (N = 69)

Variable		QD Tablet (N = 16)	QD SGC (N = 17)	BID Tablet (N = 18)	BID SGC (N = 18)	Total
Sex, N (%)	Male	3 (18.8)	2 (11.8)	3 (16.7)	7 (38.9)	15 (21.7)
	Female	13 (81.3)	15 (88.2)	15 (83.3)	11 (61.1)	54 (78.3)
Race, N (%)	White	12 (75.0)	15 (88.2)	15 (83.3)	10 (55.6)	52 (75.4)
	Black	2 (12.5)	1 (5.9)	2 (11.1)	5 (27.8)	10 (14.5)
Weight (kg)	Mean ± SD	80.7 ± 16.75	74.9 ± 9.09	79.1 ± 12.06	76.6 ± 11.61	77.8 ± 12.43
Age (years)	Mean ± SD	39.7 ± 8.47	41.6 ± 8.11	38.1 ± 11.63	37.1 ± 7.76	39.1 ± 9.12

Results continued

Pharmacokinetics

The mean (SD) observed plasma concentration vs. time profiles for the BID treatment groups are shown in Figure 2 for LPV and in Figure 3 for RTV.

Figure 2. Mean (SD) LPV Plasma Concentration-Time Profiles for BID Treatment Groups

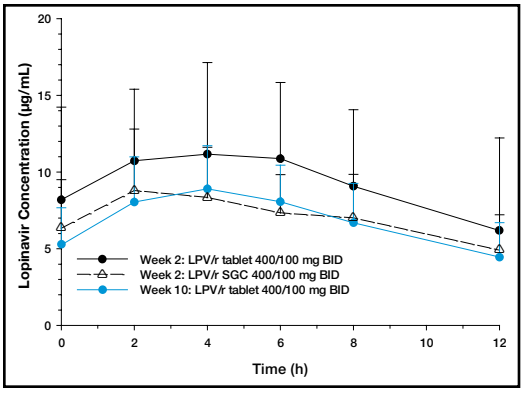
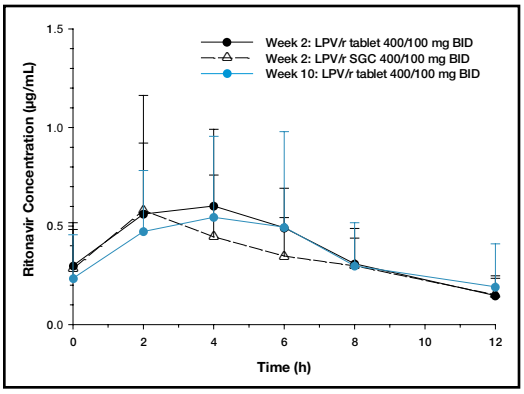


Figure 3. Mean (SD) RTV Plasma Concentration-Time Profiles for BID Treatment Groups



The mean ± SD pharmacokinetic parameters of LPV and RTV after administration of each of the BID regimens at Week 2 and Week 10 are shown in Table 2.

Table 2. LPV and RTV Pharmacokinetics for BID Treatment Groups

Pharmacokinetic Parameters (units)		Treatment Groups† Tablet BID Week 2 N = 18	SGC BID Week 2 N = 18	Tablet BID Week 10 N = 18
Lopinavir				
T_{max}	(h)	3.67 ± 1.57	3.67 ± 2.40	3.56 ± 1.62
C_{max}	(µg/mL)	12.31 ± 5.39	9.78 ± 3.67	9.90 ± 2.76
C_{min}	(µg/mL)	5.60 ± 4.52	4.46 ± 2.47	4.15 ± 2.32
C_{trough}	(µg/mL)	8.07 ± 5.68	6.34 ± 3.17	5.26 ± 2.42
AUC_{24}	(µg•h/mL)	226.4 ± 120.9	172.0 ± 62.2	169.6 ± 50.6
Ritonavir				
T_{max}	(h)	3.67 ± 1.85	4.00 ± 2.66	3.67 ± 1.71
C_{max}	(µg/mL)	0.72 ± 0.39	0.66 ± 0.54	0.67 ± 0.53
C_{min}	(µg/mL)	0.14 ± 0.08	0.14 ± 0.09	0.17 ± 0.20
C_{trough}	(µg/mL)	0.29 ± 0.18	0.28 ± 0.24	0.24 ± 0.22
AUC_{24}	(µg•h/mL)	9.64 ± 4.24	8.47 ± 5.59	9.51 ± 7.61

† Tablet BID (Week 2): LPV/r tablet 400/100 mg BID + FTC 200 mg QD + TDF 300 mg QD; SGC BID (Week 2) and Tablet BID (Week 10): LPV/r SGC 400/100 mg BID + FTC 200 mg QD + TDF 300 mg QD for 8 weeks then LPV/r tablet 400/100 mg BID + FTC 200 mg QD + TDF 300 mg QD.

Pharmacokinetics

The mean (SD) observed plasma concentration vs. time profiles for the QD treatment groups are shown in Figure 4 for LPV and in Figure 5 for RTV.

Figure 4. Mean (SD) LPV Plasma Concentration-Time Profiles for QD Treatment Groups

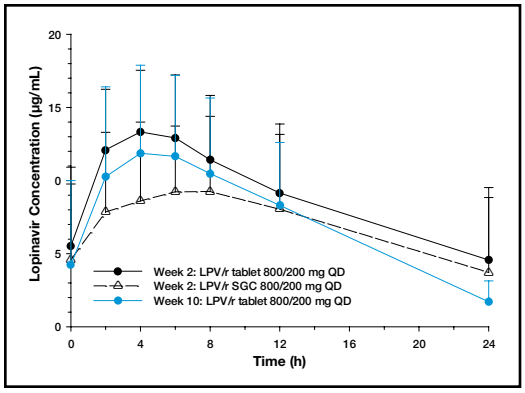
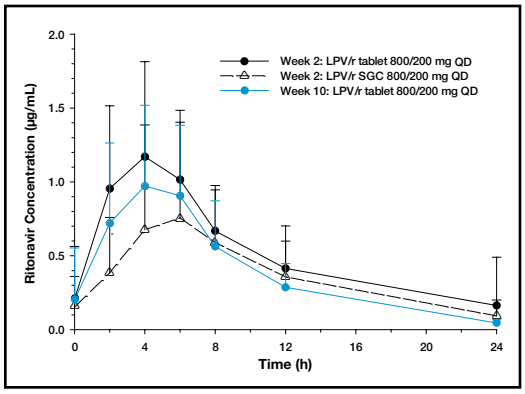


Figure 5. Mean (SD) RTV Plasma Concentration-Time Profiles for QD Treatment Groups



The mean ± SD pharmacokinetic parameters of LPV and RTV after administration of each of the QD regimens at Week 2 and Week 10 are shown in Table 3.

Table 3. LPV and RTV Pharmacokinetics for QD Treatment Groups

		Treatment Groups[a]		
Pharmacokinetic Parameters (units)		Tablet QD Week 2 N = 16[b]	SGC QD Week 2 N = 17	Tablet QD Week 10 N = 17
Lopinavir				
T_{max}	(h)	5.63 ± 5.18	8.12 ± 5.22	4.35 ± 1.62[d]
C_{max}	(µg/mL)	14.79 ± 3.46	11.31 ± 4.74[c]	13.17 ± 5.71
C_{min}	(µg/mL)	3.17 ± 3.44	2.80 ± 4.69	1.51 ± 1.46[d]
C_{trough}	(µg/mL)	5.53 ± 5.39	4.58 ± 5.18	4.23 ± 5.78
AUC_{24}	(µg•h/mL)	206.5 ± 89.7	162.7 ± 112.0[c]	168.8 ± 86.6
Ritonavir				
T_{max}	(h)	5.43 ± 5.52	7.06 ± 5.01	4.12 ± 1.32[d]
C_{max}	(µg/mL)	1.39 ± 0.48	1.09 ± 0.75	1.14 ± 0.58
C_{min}	(µg/mL)	0.06 ± 0.04	0.06 ± 0.07	0.04 ± 0.02
C_{trough}	(µg/mL)	0.21 ± 0.37	0.15 ± 0.21	0.20 ± 0.35
AUC_{24}	(µg•h/mL)	11.74 ± 5.04	8.44 ± 3.84	9.22 ± 4.13

[a] Tablet QD (Week 2): LPV/r tablet 800/200 mg QD + FTC 200 mg QD + TDF 300 mg QD; SGC QD (Week 2) and Tablet QD (Week 10): LPV/r SGC 800/200 mg QD + FTC 200 mg QD + TDF 300 mg QD for 8 weeks then LPV/r tablet 800/200 mg QD + FTC 200 mg QD + TDF 300 mg QD.

[b] N=14 for Tablet QD RTV results due to lab error.

[c] Statistically significantly different from Tablet QD, Week 2 results (ANOVA; $p < 0.05$).

[d] Statistically significantly different from SGC QD, Week 2 results (linear mixed effects model, $p < 0.05$).

The LPV relative bioavailabilities of the tablet compared to the SGC (for the BID and QD treatment groups) for Week 2 are shown in Table 4.

Table 4. Least Square Means and 90% Confidence Intervals of LPV Pharmacokinetic Parameters at Week 2

		Central Value[a]		Relative Bioavailability	
Test vs. Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate[b]	90% Confidence Interval
BID: Tablet vs. SGC	C_{max}	11.41	9.201	1.240	1.017–1.512
	C_{min}	4.251	3.745	1.135	0.682–1.890
	C_{trough}	6.551	5.478	1.196	0.753–1.900
	AUC_{24}	202.8	162.0	1.252	0.983–1.595
QD: Tablet vs. SGC	C_{max}	14.42	10.44	1.381	1.123–1.699
	C_{min}	1.816	1.523	1.192	0.700–2.031
	C_{trough}	3.802	2.821	1.348	0.831–2.186
	AUC_{24}	191.6	141.3	1.356	1.053–1.746

[a] Antilogarithm of the least squares means for logarithms.

[b] Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

The RTV relative bioavailabilities of the tablet compared to the SGC (for the BID and QD treatment groups) for Week 2 are shown in Table 5.

Table 5. Least Square Means and 90% Confidence Intervals of RTV Pharmacokinetic Parameters at Week 2

		Central Value[a]		Relative Bioavailability	
Test vs. Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate[b]	90% Confidence Interval
BID: Tablet vs. SGC	C_{max}	0.637	0.511	1.246	0.881–1.763
	C_{min}	0.112	0.113	0.997	0.670–1.483
	C_{trough}	0.230	0.208	1.104	0.651–1.871
	AUC_{24}	8.585	7.143	1.202	0.887–1.629
QD: Tablet vs. SGC	C_{max}	1.306	0.846	1.543	1.060–2.246
	C_{min}	0.044	0.046	0.961	0.625–1.477
	C_{trough}	0.094	0.086	1.099	0.621–1.946
	AUC_{24}	10.57	7.462	1.417	1.019–1.969

[a] Antilogarithm of the least squares means for logarithms.

[b] Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

- Following multiple-dose administration of LPV/r in a parallel group comparison (Week 2), LPV concentrations are approximately 14% to 25% higher following BID administration of the tablet compared to the SGC and 19% to 38% higher following QD administration of the tablet compared to the SGC.
- RTV C_{max} and AUC_{24} were increased 25% and 54% following BID and QD dosing, respectively, when the LPV/r tablet was compared to the SGC.
- RTV C_{trough} and C_{min} were similar between the tablet and SGC formulations for both BID and QD dosing.

Results continued

The LPV relative bioavailabilities of the tablet compared to the SGC (for the BID and QD treatment groups) for Week 10 vs. Week 2 are shown in Table 6.

Table 6. Least Square Means and 90% Confidence Intervals of LPV Pharmacokinetic Parameters, Week 10 vs. Week 2

		Central Value[a]		Relative Bioavailability	
Test vs. Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate[b]	90% Confidence Interval
BID: Tablet vs. SGC	C_{max}	9.535	9.201	1.036	0.900–1.193
	C_{min}	3.057	3.745	0.816	0.481–1.385
	C_{trough}	4.096	5.478	0.748	0.375–1.491
	AUC_{24}	162.0	162.0	1.000	0.853–1.173
QD: Tablet vs. SGC	C_{max}	12.15	10.44	1.163	1.007–1.344
	C_{min}	0.765	1.523	0.502	0.291–0.866
	C_{trough}	1.526	2.821	0.541	0.266–1.101
	AUC_{24}	152.3	141.3	1.078	0.915–1.270

[a] Antilogarithm of the least squares means for logarithms.
[b] Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

The RTV relative bioavailabilities of the tablet compared to the SGC (for the BID and QD treatment groups) for Week 10 vs. Week 2 are shown in Table 7.

Table 7. Least Square Means and 90% Confidence Intervals of RTV Pharmacokinetic Parameters, Week 10 vs. Week 2

		Central Value[a]		Relative Bioavailability	
Test vs. Reference	Pharmacokinetic Parameter	Test	Reference	Point Estimate[b]	90% Confidence Interval
BID: Tablet vs. SGC	C_{max}	0.549	0.511	1.076	0.829–1.396
	C_{min}	0.112	0.113	0.992	0.682–1.444
	C_{trough}	0.167	0.208	0.801	0.439–1.462
	AUC_{24}	7.824	7.143	1.095	0.907–1.323
QD: Tablet vs. SGC	C_{max}	0.996	0.846	1.177	0.900–1.539
	C_{min}	0.033	0.046	0.712	0.484–1.047
	C_{trough}	0.069	0.086	0.808	0.435–1.502
	AUC_{24}	8.334	7.462	1.117	0.920–1.356

[a] Antilogarithm of the least squares means for logarithms.
[b] Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

- In a within-subject analysis comparing the tablet at Week 10 to the SGC at Week 2, LPV and RTV concentrations were similar.
- The maximum average differences between the tablet and SGC following BID and QD dosing were 4% and 16%, respectively, for LPV and 10% and 18%, respectively, for RTV.
- LPV C_{trough} and C_{min} were 18% to 25% lower and 46% to 50% lower following BID and QD dosing, respectively, with the tablet compared to the SGC.

Overall Conclusions

- Modest increases in LPV exposure with the tablet formulation relative to the SGC formulation in HIV-infected subjects in the parallel group comparison were consistent with previous observations in healthy volunteers.
  - As previously reported, the tablet formulation was not associated with increased rates of adverse events or laboratory abnormalities.[3]
- In the within-subject analysis, LPV C_{max} and AUC were similar with the tablet and SGC formulations. LPV C_{min} and C_{trough} were modestly lower following administration of the tablet compared to the SGC.
- Antiviral activity of the tablet formulation dosed QD and BID was similar through 48 weeks of therapy. Similarly, response was independent of baseline viral load or CD4 T-cell count.[3]

References

1. Danner SA, Carr A, Leonard JM, et al. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. *N Eng J Med*. 1995;333:1528-33.
2. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Eng J Med*. 1998;338:853-60.
3. Gathe J et al. Study M05-730 Primary Efficacy Results at Week 48: Phase 3, Randomized, Open-Label Study of Lopinavir/ritonavir (LPV/r) Tablets Once Daily (QD) versus Twice Daily (BID), Co-Administered with Tenofovir DF (TDF) + Emtricitabine (FTC) in Antiretroviral-Naïve (ARV) HIV-1 Infected Subjects. 15th Conference on Retroviruses and Opportunistic Infections, 2008, Poster 775.