Poster 570

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Once-Daily vs. Twice-Daily Lopinavir/ritonavir in Antiretroviral-Naïve Patients: 48-Week Results

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BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir (r), which functions as a pharmacokinetic enhancer. LPV/r is marketed as Kaletra®. The approved adult dose of LPV/r is 400/100 mg twice daily (BID). Antiviral activity of LPV/r has been demonstrated in antiretroviral (ARV)-naïve and PI-experienced patients. In a phase 2 study of LPV/r in combination with stavudine (d4T) and lamivudine (3TC) in ARV-naïve patients (Study 720), 67% of patients maintained HIV RNA <400 copies/mL through 5 years.[1]

A once-daily (QD) ARV regimen including LPV/r may offer an advantage with regard to convenience while maintaining antiviral potency in ARV-naïve patients. In a pilot study (Study 056), ARV-naïve, HIV-infected adults (N=38) received LPV/r 800/200 mg QD or 400/100 mg BID with d4T and 3TC given BID.[2,3] LPV/r 800/200 mg QD produced similar C_{max} and AUC and lower and more variable C_{trough} compared to 400/100 mg BID. However, virologic response through 72 weeks was similar.[3] Further, the Inhibitory Quotient (IQ; C_{trough}/IC_{50} for wild type HIV) achieved with once-daily LPV/r compares favorably to that of other QD PIs.[4]

Based on these pilot results, Study 418 was initiated to further assess the pharmacokinetics, antiviral activity and safety of a once daily dosing regimen for LPV/r in ARV-naïve patients. In Study 418, patients received LPV/r with tenofovir DF (TDF) 300 mg and emtricitabine (FTC) 200 mg once daily. Patients receiving LPV/r 800/200 mg QD demonstrated slightly higher lopinavir C_{max}, similar AUC, and lower C_{trough} compared to 400/100 mg BID.[5] The median IQ was 49 for QD and 94 for BID.

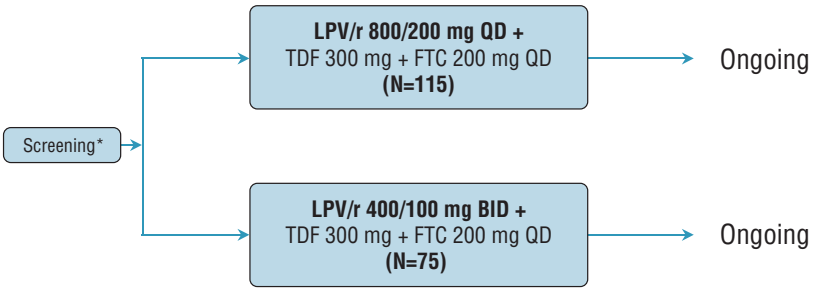
This analysis presents the comparative safety and efficacy through 48 weeks.

METHODS

Study 418 is the first trial of an entirely once-daily LPV/r-based regimen (Figure 1).

- Randomized, open-label, multi-center, international study.
- Patients were ARV-naïve, with HIV RNA >1,000 copies/mL and any CD4 count.
- 190 patients were randomized 3:2 to LPV/r 800/200 mg QD (n=115) or 400/100 mg BID (n=75).
- All patients also received TDF 300 mg and FTC 200 mg once daily.

Figure 1. Study 418 Schematic



* Patients were randomized in a 3:2 ratio to one of two study arms; baseline adherence was assessed over a 5-7 day placebo lead-in period.

Analysis

- HIV RNA levels were assessed using Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitative PCR Assay, Version 1.5 (limit of quantitation, 50 copies/mL).
- The proportion of patients with HIV RNA below 50 copies/mL was assessed using an intent-to-treat, noncompleter=failure (ITT NC=F) method, in which missing values were considered failure unless the immediately preceding and following values were below 50 copies/mL. An observed data (OD) method was also used, in which missing values were excluded from the analysis. The 95% confidence interval for the difference in response rates was assessed based on the binomial distribution.
- For each HIV RNA result above 500 copies/mL between Weeks 12-24, isolates were submitted for genotypic resistance testing, as were corresponding baseline isolates for each patient. Resistance to lopinavir was defined as the emergence of any primary or active site mutation in protease (positions 8, 30, 32, 46, 47, 48, 50, 82, 84, 90). Resistance to tenofovir and emtricitabine were defined by the presence of K65R and M184V/I mutations in reverse transcriptase, respectively.

- Cumulative incidence of adverse events through 48 weeks was summarized.
- Fasting laboratory determinations, including directly measured LDL and HDL cholesterol values, were obtained at baseline and Week 48.
- For patients remaining on study for 48 weeks, the impact of lipid changes and blood pressure on 10-year coronary heart disease (CHD) risk were calculated based on the results of the Framingham Heart Study, which also takes into consideration gender, age, history of diabetes mellitus (DM) and smoking status.[6]

RESULTS

Baseline Characteristics

- Demographics and baseline disease characteristics were similar between treatment groups, with over 20% female and about 45% non-Caucasian patients (Table 1).
- The patient population was relatively advanced, as approximately 45% of patients had baseline CD4 count below 200 cells/mm^3 and 38% had baseline HIV RNA above 100,000 copies/mL.
- The overall mean baseline viral load was approximately 65,000 copies/mL.

Table 1. Study 418: Baseline Characteristics

	LPV/r 800/200 QD (n=115)	LPV/r 400/100 BID (n=75)
Gender		
Male	81%	75%
Female	19%	25%
Age (years)		
Mean (range)	39 (19-75)	38 (19-75)
Race		
Caucasian	56%	51%
Black	27%	36%
Hispanic	10%	5%
Other	7%	8%
HIV RNA (log_{10} copies/mL)		
Median (IQR)	4.8 (4.3-5.5)	4.6 (4.3-5.3)
Range	3.5-6.4	2.6-6.2
CD4 count (cells/mm^3)		
Median (IQR)	214 (116-380)	232 (95-339)
Below 200 cells/mm^3	44%	47%

Efficacy

- In the ITT (NC=F) analysis (Figure 2) and the OD analysis (Figure 3), a similar proportion of patients achieved HIV RNA below 50 copies/mL through 48 weeks.
- Based on the ITT (NC=F) analysis, the 95% confidence interval for the difference (QD minus BID) in Week 48 response proportions was (-7%, 20%), confirming the noninferiority of the QD regimen compared to the BID regimen through 48 weeks.
- Results of genotypic testing were available for 5 patients in each group with HIV RNA >500 copies/mL occurring at any time during Weeks 12-24. No patient demonstrated lopinavir or tenofovir resistance, and only 1 patient in each group demonstrated FTC resistance.
- CD4 cell count mean increases from baseline were comparable between treatment groups (Figure 4).

Figure 2. Study 418: HIV RNA <50 copies/mL (ITT NC=F)

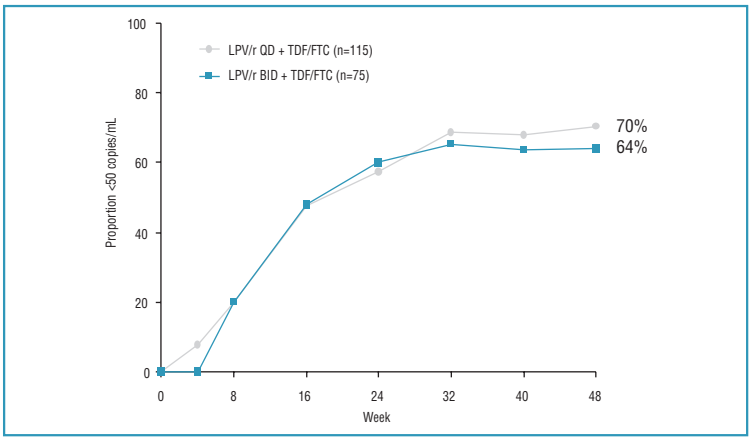


Figure 3. Study 418: HIV RNA <50 copies/mL (Observed Data)

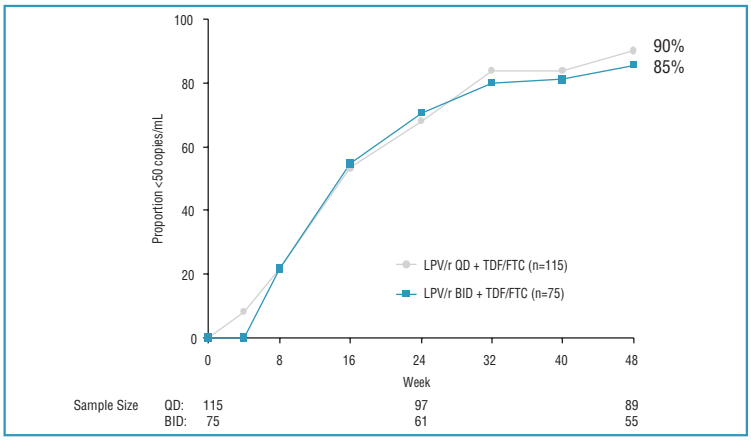
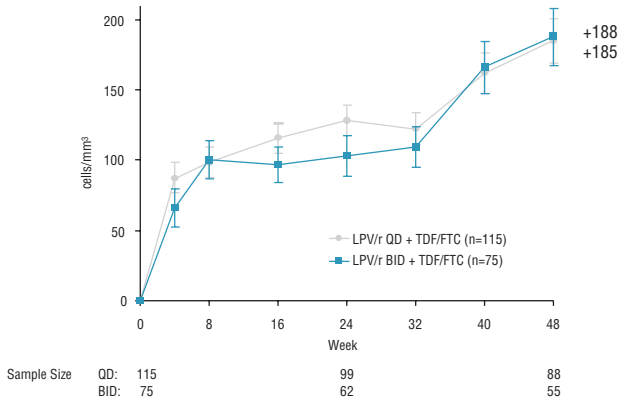


Figure 4. Study 418: CD4 Cell Count Mean (±SE) Change from Baseline



Safety

Patient Disposition

- Reasons for premature discontinuation prior to Week 48 are summarized in Table 2.
- A higher rate of discontinuations due to adverse events was observed in the QD group, while higher rates of loss to follow-up and nonadherence were observed in the BID group.
- Adverse events resulting in discontinuation were generally gastrointestinal in nature. One patient in the BID group on chronic prednisone therapy for myositis died of multi-organ failure after 6 weeks on study, following a diagnosis of adenocarcinoma. The event was considered unrelated to study drugs.

Table 2. Study 418: Disposition Through Week 48

	LPV/r 800/200 mg QD (n=115)	LPV/r 400/100 mg BID (n=75)
Patients discontinued	**22 (19%)**	**19 (25%)**
Adverse event	14 (12%)	4 (5%)
Death	0 (0%)	1 (1%)
Virologic failure	0 (0%)	1 (1%)
Lost to follow-up	3 (3%)	6 (8%)
Withdrew consent	4 (3%)	4 (5%)
Nonadherence	1 (1%)	3 (4%)

Adverse Events/Laboratory Abnormalities

- Moderate/severe, drug-related adverse events and grade 3/4 lab abnormalities occurring in >3% of patients in either treatment group are shown in Table 3.

Table 3. Study 418: Most Common Adverse Events and Grade 3/4 Laboratory Abnormalities

Moderate or Severe LPV/r-Related Adverse Events or Grade 3/4 Lab Abnormality*	LPV/r 800/200 mg QD (n=115)	LPV/r 400/100 mg BID (n=75)	p-value
Diarrhea	16%	5%	0.04
Nausea	9%	8%	ns
Vomiting	3%	4%	ns
SGOT/AST (>5 x ULN)	5%	3%	ns
SGPT/ALT (>5 x ULN)	4%	3%	ns
Triglycerides (>750 mg/dL)	5%	4%	ns
Amylase (>2 x ULN)	7%	5%	ns

- Overall, 98% of patients demonstrated maximum creatinine ≤1.5 mg/dL. One subject in each group demonstrated creatinine >3.0 mg/dL (acute renal failure – ARF). One case of ARF occurred at Week 34 in a 75-year-old male patient with a baseline creatinine clearance of 40 mL/min who was started on full dose TDF. More recent dosing guidelines recommend that TDF be dosed every other day in this circumstance. Renal biopsy demonstrated non-specific changes with some renal tubules showing focal degenerative signs (cytoplasmic vacuolization). The second case of ARF occurred at Week 38 in a 54-year-old male patient, requiring temporary hemodialysis. Renal biopsy demonstrated tubulointerstitial nephritis. Both patients experienced improvement off study drug with creatinine levels returning to ≤1.7 mg/dL.

Table 4. Study 418: Mean Change from Baseline in Lipid Values

	Study 418: LPV/r 800/200 mg QD + TDF/FTC (n=89)		Study 418: LPV/r 400/100 mg BID + TDF/FTC (n=54)		Study 863[7]: LPV/r 400/100 mg BID + d4T/3TC (n=269)	
Variable	**Baseline**	**Change to Week 48**	**Baseline**	**Change to Week 48**	**Baseline**	**Change to Week 48**
Total Cholesterol (mg/dL)	159	+27	168	+27	158	+53
HDL Cholesterol (mg/dL)	40	+3	42	+6	nd	nd
LDL Cholesterol (mg/dL)	96	+14	102	+13	nd	nd
Triglycerides (mg/dL)	137	+82	136	+76	166	+125

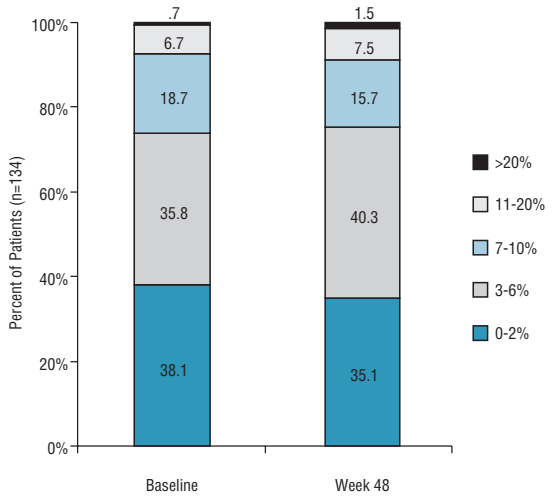
nd = not done

- Mean lipid value changes from baseline to Week 48 appeared lower in Study 418 vs. Study 863[7] (Table 4), perhaps due to different NRTI regimens. All increases shown were statistically significant.
- At baseline, 3 subjects were using lipid-lowering agents. Through 48 weeks of therapy, one additional subject in each treatment group initiated lipid-lowering therapy.

RESULTS *continued*

- Overall, the mean 10-year CHD risk did not change significantly from baseline (4.6%) to Week 48 (5.0%) and analysis of risk rates by category likewise did not indicate increased CHD risk from baseline to Week 48 (Figure 5).

Figure 5. Study 418: 10-year CHD Risk (Based on Framingham Heart Study)



CONCLUSIONS

- At Week 48, by intent-to-treat analysis with noncompleters considered failures, 70% of patients in the QD LPV/r+TDF+FTC regimen demonstrated HIV RNA <50 copies/mL, compared to 64% for the same regimen with LPV/r dosed BID + TDF + FTC (p=0.35).
- Noninferiority of the LPV/r QD regimen compared to LPV/r BID-based regimen (ITT NC=F) was confirmed by the 95% confidence interval for the difference (QD minus BID) in response proportions (-7% to 20%).
- Gastrointestinal events were the most common adverse events, with a higher rate of diarrhea in the QD arm.
- Lipid elevations were the most common laboratory abnormality, although these did not result in significant changes to the 10-year coronary heart disease risk based on Framingham Heart Study calculations.

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