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Once-Daily vs.Twice-Daily Lopinavir/ritonavir in Antiretroviral-Naïve Patients: 96-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). In the U.S., adult dose of LPV/r 800/200 mg once-daily (QD) is also approved for antiretroviral-naïve patients. Antiviral activity of LPV/r has been demonstrated in antiretroviral-naïve and PI-experienced patients.

A once-daily antiretroviral regimen including LPV/r may offer an advantage with regard to convenience while maintaining antiviral potency in antiretroviral-naïve patients. In a pilot study (Study 056), antiretroviral-naïve, HIV-1-infected adults (N=38) received LPV/r 800/200 mg QD or 400/100 mg BID with stavudine and lamivudine given BID.[1,2] 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.[2] Further, the inhibitory quotient (IQ; C_{trough}/IC_{50} for wild-type HIV-1) achieved with once-daily LPV/r compares favorably to that of other QD PIs.[3]

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 antiretroviral-naïve patients. In Study 418, subjects received LPV/r with tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg once-daily. Subjects 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.[4] The median IQ was 49 for QD and 94 for BID.

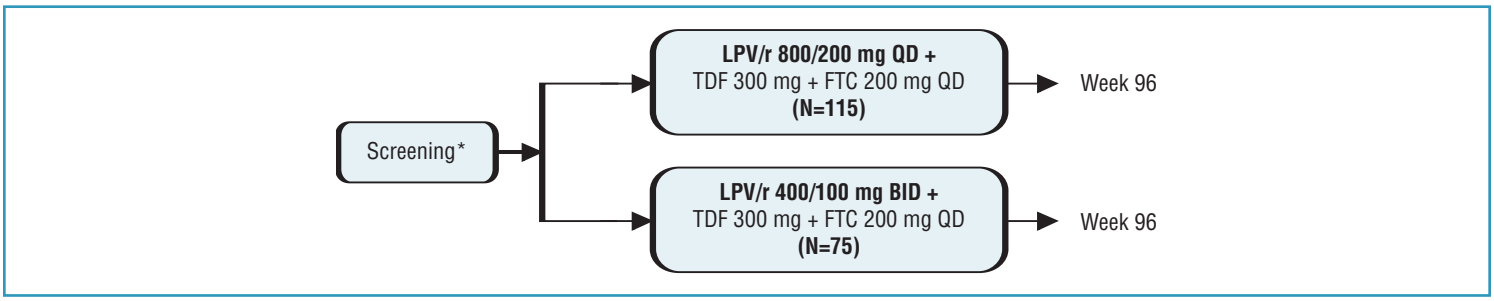
Analysis of the comparative safety and efficacy through 48 weeks showed noninferiority of the LPV/r QD regimen compared to the LPV/r BID regimen, with a higher rate of diarrhea in the LPV/r QD arm.[5] This analysis presents the comparative safety and efficacy through 96 weeks.

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.
- Subjects were antiretroviral-naïve, with plasma HIV-1 RNA >1,000 copies/mL and any CD4 count.
- 190 subjects were randomized 3:2 to LPV/r 800/200 mg QD (n=115) or 400/100 mg BID (n=75).
- All subjects also received TDF 300 mg and FTC 200 mg QD.

Figure 1. Study 418 Schematic



* Subjects 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

- Plasma HIV-1 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 subjects with HIV-1 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.
- Analysis was also conducted using the U.S. FDA time-to-loss of virologic response (TLOVR) algorithm, in which subjects are considered responders if they achieve two consecutive HIV-1 RNA levels <50 copies/mL and maintain the levels through the timepoint of interest. Subjects who subsequently demonstrate two consecutive rebound HIV-1 RNA levels >50 copies/mL or who discontinue from the study are considered non-responders.
- For each HIV-1 RNA result above 500 copies/mL between Weeks 12–96, isolates were submitted for genotypic resistance testing, as were corresponding baseline isolates for each subject. Resistance to lopinavir was defined as the emergence of any mutation at protease amino acid 8, 30, 32, 46, 47, 48, 50, 82, 84 or 90 with corresponding phenotypic lopinavir resistance of at least 2.5-fold versus wild-type. Resistance to TDF was defined by the development of any new mutation at amino acid 41, 65, 67, 70, 210, 215, 219 or the 69 insertion mutation in reverse transcriptase. Resistance to FTC was defined by the development of the M184V/I/T mutation in reverse transcriptase.
- Cumulative incidence of adverse events through 96 weeks was summarized.

Baseline Characteristics

- Demographics and baseline disease characteristics were similar between treatment groups, with over 20% female and about 45% non-Caucasian subjects (Table 1).

Table 1. Study 418: Baseline Characteristics

	LPV/r 800/200 mg QD (n=115)	LPV/r 400/100 mg BID (n=75)
Gender		
Male	81%	75%
Female	19%	25%
Age (years)		
Mean (range)	39 (19–75)	38 (19–75)
Race		
Caucasian	57%	51%
Black	27%	36%
Hispanic	10%	5%
Other	6%	8%
HIV-1 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%

- The study population had relatively advanced HIV disease, as approximately 45% of subjects had baseline CD4 count below 200 cells/mm^3, including 16% with CD4 count below 50 cells/mm^3, and 38% had baseline HIV-1 RNA above 100,000 copies/mL.
- The overall mean baseline viral load was approximately 65,000 copies/mL.

Efficacy

- In the ITT (NC=F) analysis (Figure 2) and the OD analysis (Figure 3), a similar proportion of subjects achieved HIV-1 RNA below 50 copies/mL through 96 weeks.

Figure 2. Study 418: HIV-1 RNA <50 copies/mL (ITT NC=F)

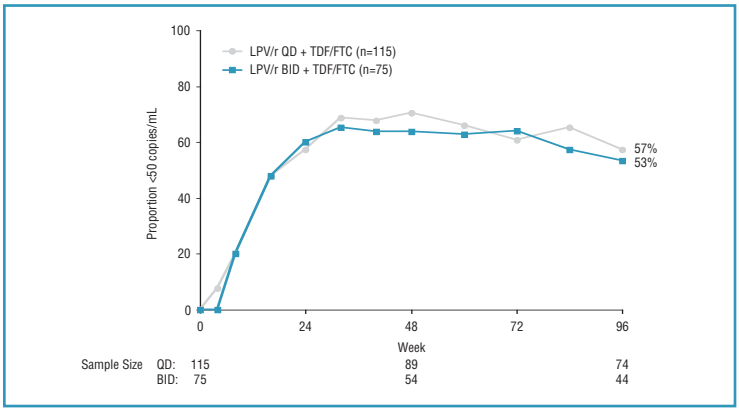
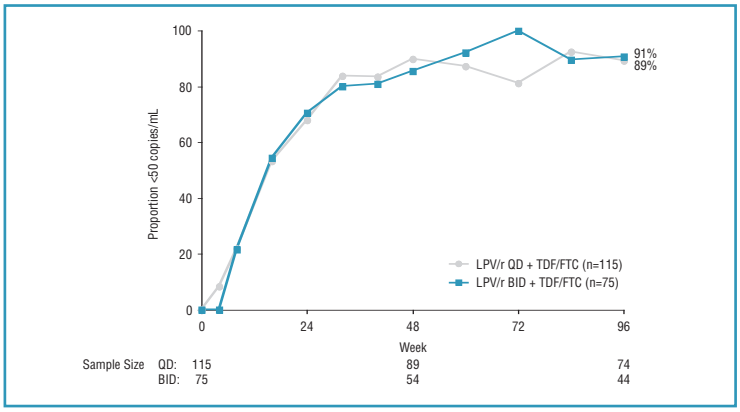


Figure 3. Study 418: HIV-1 RNA <50 copies/mL (Observed Data)



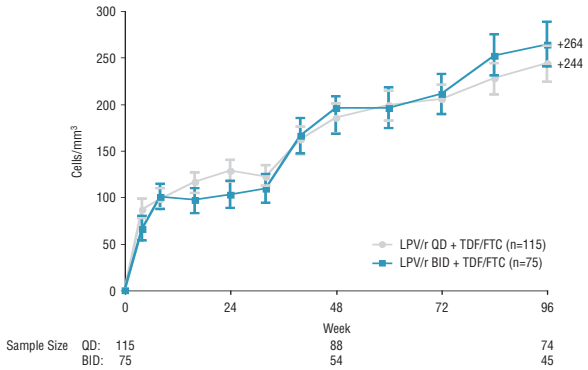
- By FDA TLOVR analysis, Week 96 response rates were 57% QD and 55% BID.
- Based on the ITT (NC=F) analysis, the 95% confidence interval for the difference (QD minus BID) in Week 96 response proportions was (–10%, 19%).
- Results of genotypic testing were available for 23 subjects with HIV-1 RNA >500 copies/mL occurring at any time during Weeks 12–96. No subject demonstrated LPV or TDF resistance, and only 4 subjects demonstrated FTC resistance (Table 2).

Table 2. Study 418: Genotypic Testing Through Week 96

	LPV/r 800/200 mg QD (n=115)	LPV/r 400/100 mg BID (n=75)
Subjects qualifying for resistance testing	17 (15%)	11 (15%)
Genotypic results available	15/17	8/11
LPV resistance	0/15	0/8
TDF resistance	0/15	0/8
FTC resistance	3/15	1/8

- CD4 cell count mean increases from baseline were comparable between treatment groups (Figure 4).

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



Safety

Subject Disposition

- Reasons for premature discontinuation prior to Week 96 are summarized in Table 3.

Table 3. Study 418: Disposition Through Week 96

	LPV/r 800/200 mg QD (n=115)	LPV/r 400/100 mg BID (n=75)
Subjects discontinued	42 (37%)	29 (39%)
Adverse event	20 (17%)	7 (9%)
Death	0 (0%)	1 (1%)
Virologic failure	0 (0%)	2 (3%)
Lost to follow-up	9 (8%)	10 (13%)
Withdrew consent	5 (4%)	5 (7%)
Nonadherence	5 (4%)	3 (4%)
Other	3 (3%)	1 (1%)

- A higher rate of discontinuations due to adverse events was observed in the QD group, while higher rates of loss to follow-up were observed in the BID group.
- Adverse events resulting in discontinuation were generally gastrointestinal in nature. One subject 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.

Adverse Events/Laboratory Abnormalities

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

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

	Cumulative Incidence Through 96 Weeks				
Moderate or Severe LPV/r-Related Adverse Events or Grade 3 or 4 Lab Abnormality	LPV/r 800/200 mg QD (n=115)	LPV/r 400/100 mg BID (n=75)	P-value Comparing Incidence Rates	Prevalence at Week 96 (800/200 mg QD, n=77)	Prevalence at Week 96 (400/100 mg BID, n=46)
Diarrhea	17%	5%	0.014	3%	0
Nausea	9%	8%	ns	0	0
Vomiting	3%	4%	ns	0	0
SGOT/AST (>5 x ULN)	7%	3%	ns	1%	0
SGPT/ALT (>5 x ULN)	5%	3%	ns	1%	0
Triglycerides (>750 mg/dL)	6%	7%	ns	1%	2%
Amylase (>2 x ULN)	8%	7%	ns	0	0
Cholesterol (>300 mg/dL)	4%	6%	ns	1%	0

- At Week 96, a majority of subjects had total cholesterol <200 mg/dL or triglycerides <250 mg/dL (Table 5).

Table 5. Study 418: Summary of Lipid Values at Week 96

Category	LPV/r 800/200 mg QD (n=77)	LPV/r 400/100 mg BID (n=46)
Total cholesterol (mg/dL)		
<200	50 (65%)	22 (48%)
>200 to 240	21 (27%)	17 (37%)
>240 to 300	5 (6%)	7 (15%)
>300 to 400	1 (1%)	0
>400	0	0
Triglycerides (mg/dL)		
<250	59 (77%)	39 (85%)
>250 to 400	15 (19%)	5 (11%)
>400 to 750	2 (3%)	1 (2%)
>750 to 1200	1 (1%)	1 (2%)
>1200	0	0

Overall for 98% of subjects, the maximum creatinine value was ≤1.5 mg/dL. One subject in each group demonstrated creatinine >3.0 mg/dL (acute renal failure – ARF).

- ARF occurred at Week 38 in a 54-year-old male subject who required temporary hemodialysis. Renal biopsy demonstrated tubulointerstitial nephritis. The subject discontinued the study and creatinine levels returned to near normal.
- ARF occurred at Week 34 in a 75-year-old male subject with a baseline creatinine clearance of 40 mL/min who was begun on full dose TDF. The subject received one hemodialysis session. Renal biopsy demonstrated non-specific changes with focal degenerative signs (cytoplasmic vacuolization) in some renal tubules. LPV/r was restarted but TDF was replaced by stavudine 30 mg BID and the dose of emtricitabine was reduced to 200 mg every 72 hours. His creatinine level continued to decrease. TDF dosing recommendations implemented after initiation of this study indicate that every other day dosing of TDF would have been most appropriate for this subject based on creatinine clearance.
- No subject demonstrated a new creatinine elevation >1.5 mg/dL after Week 48.

CONCLUSIONS

- At Week 96, by intent-to-treat analysis with noncompleters considered failures, 57% of subjects in the QD LPV/r+TDF+FTC regimen demonstrated HIV-1 RNA <50 copies/mL, compared to 53% for the regimen of BID LPV/r with QD TDF + FTC (p=0.58).
- Through 96 weeks, 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 (–10% to 19%).
- No subject developed LPV or TDF resistance through 96 weeks.
- In this study with the soft gel capsule formulation of LPV/r, gastrointestinal events were the most common adverse events, with a higher rate of diarrhea in the QD arm.

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