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Higher Doses of Lopinavir/ritonavir (LPV/r) in Highly Treatment-Experienced, HIV-Infected Patients: 48-Week Safety/Efficacy Evaluation

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BACKGROUND

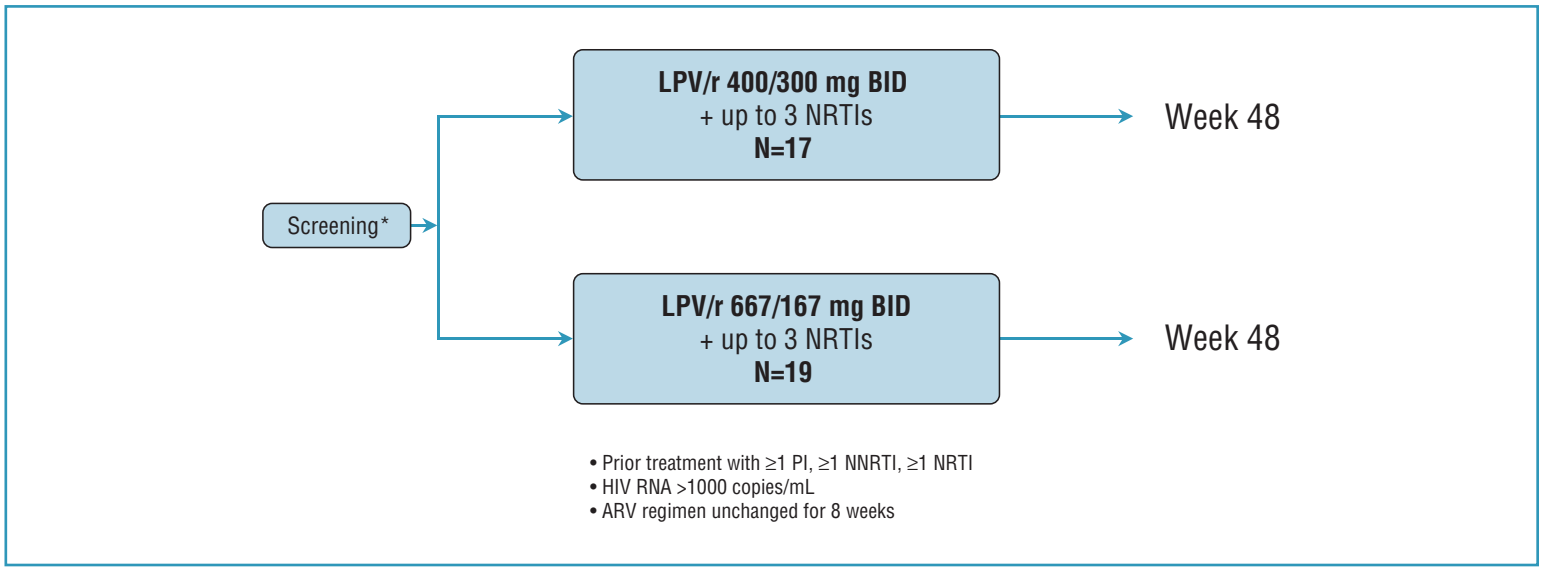
Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir (RTV), which functions as a pharmacokinetic enhancer, and is marketed as Kaletra® (LPV/r). The approved dose of LPV/r is 400/100 mg (3 capsules) twice daily (BID). Antiviral activity of LPV/r has been demonstrated in antiretroviral (ARV)-naive and PI-experienced, NNRTI-naive patients.[1-4]

However, high-level drug resistance is likely in patients failing multiple antiretroviral regimens. Higher doses of LPV/r may provide LPV concentrations sufficient to overcome certain degrees of reduced LPV phenotypic susceptibility, resulting in a significant treatment effect.

METHODS

Study 049 was an open-label, multi-center study exploring the safety, pharmacokinetics and efficacy of higher doses of LPV/r in patients who failed multiple prior therapeutic regimens (Figure 1). Two strategies were employed to increase LPV plasma concentration. One regimen consisted of standard dose LPV/r (400/100 mg BID) with 200 mg BID additional RTV (400/300 mg BID), while the other group received 5 co-formulated capsules (667/167 mg) of LPV/r BID.

Figure 1. Study 049 Design



HIV RNA levels were assessed using the Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitative PCR Assay, Version 1.5 [lower limit of quantitation (LLOQ), 50 copies/mL].

Mean changes from baseline over time in HIV RNA level and CD4 cell count were analyzed, and the maximum change from baseline (BL) in HIV RNA level was assessed.

The proportion of patients with HIV RNA below 50 copies/mL was assessed by two methods:

- On-Treatment: Missing values were excluded from the analysis.
- Intent-to-Treat — Noncompleter=Failure (ITT NC=F): Any subject with a missing value at a visit was considered above the LLOQ unless the values immediately preceding and immediately following were below the LLOQ.

Cumulative incidence of adverse events and laboratory abnormalities through 48 weeks were summarized.

RESULTS

Demographics and Baseline Characteristics

- A total of 36 patients were enrolled. Seventeen patients received LPV/r 400/300 mg BID, and nineteen patients received LPV/r 667/167 mg BID.
- No statistically significant or clinically meaningful differences were observed between treatment groups with respect to demographic and baseline characteristics.
- Patients were primarily male (83%) and Caucasian (75%), with a mean age of 41 years.
- Seven patients (3 in the 400/300 mg BID group and 4 in the 667/167 mg BID group) were positive at baseline for anti-HCV antibodies. No subject was positive for Hepatitis B surface antigen.
- Median baseline HIV RNA level and CD4 cell count were 4.7 $\log_{10}$ copies/mL (range 3.21–5.88) and 96 cells/mm^3 (range 2-642), respectively.
- Patients had been treated with a median of 4 PIs (range 1-5), and 78% had been treated with at least 3 prior PIs. The median fold change in LPV phenotypic susceptibility relative to wild type HIV was 4.5 (range 0.6-273).
- The median number of pre-study NRTIs and NNRTIs was 5 (range 2-7) and 1 (range 0-3), respectively. The most commonly used NRTIs within the study were didanosine (58%), lamivudine (42%), stavudine (42%), and abacavir (36%).

Pharmacokinetic/Pharmacodynamic Analysis

- As reported previously,[5] LPV trough concentrations were similar between regimens and were 60-70% higher compared to LPV/r 400/100 mg BID. Adding 200 mg RTV BID increased RTV exposure by about 6-fold and increasing LPV/r by 267/67 (2 capsules) mg BID increased RTV exposure by about 2-fold relative to RTV exposures achieved with LPV/r 400/100 mg BID.
- Median LPV inhibitory quotient (IQ, ratio of LPV trough concentration to baseline fold change in LPV phenotypic susceptibility relative to wild type HIV) was 27 (range 0.7 to 438).
- In a multivariable PK/PD analysis, higher LPV IQ, more active NRTIs, and lowerBL HIV RNA were associated with higher probability of achieving HIV RNA <400 c/mL through 48 weeks of therapy.[6]

Patient Disposition

- Twenty patients discontinued prior to Week 48, most commonly due to adverse events (n=7) and virologic failure (n=5) (Table 1).
- Adverse events leading to discontinuation included fever; nausea and vomiting (n=2); and asthenia, vomiting, and dizziness in the 400/300 mg group, and nausea, taste loss, and parosmia; gluteal tendonitis; and elevated liver function tests in the 667/167 mg group.

Table 1. Patient Disposition Through 48 Weeks

	Number of Subjects	
Reason for Discontinuation	400 mg/300 mg BID (N=17)	667 mg/167 mg BID (N=19)
Adverse Event/HIV-related event	4	3
Virologic Failure	4	1
Noncompliance	0	3
Lost to follow up	1	1
Personal reasons	1	0
Prohibited medication	0	1
Other*	1	0

*Subject was diagnosed as end-stage HIV infection. Patient and primary care physician elected to discontinue study.

Efficacy

- The overall mean change in HIV RNA from baseline to Week 48 was –1.9 $\log_{10}$ copies/mL, with no significant difference between treatment groups (Figure 2).
- Among 35 patients with at least one HIV RNA value after baseline, 21 (60%) had HIV RNA <400 c/mL at least once (56% 400/300 mg BID, 63% 667/167 mg BID), and 29 (83%) had a decrease from BL of at least 1.0 $\log_{10}$ c/mL (Figure 3).

Figure 2. Mean Change from Baseline in HIV RNA

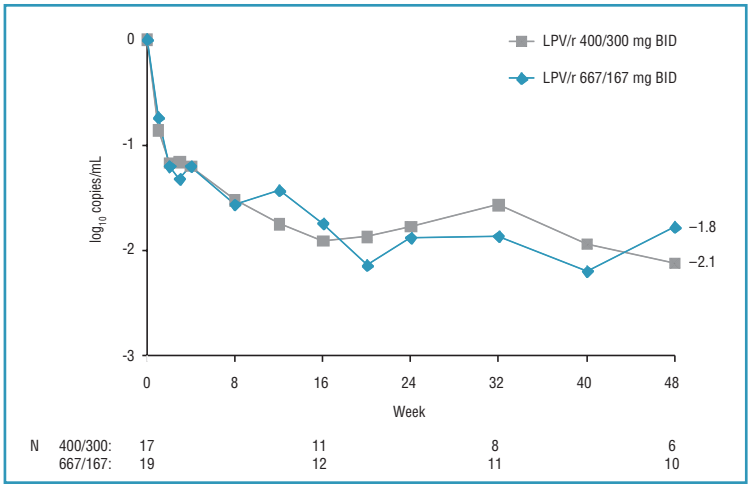
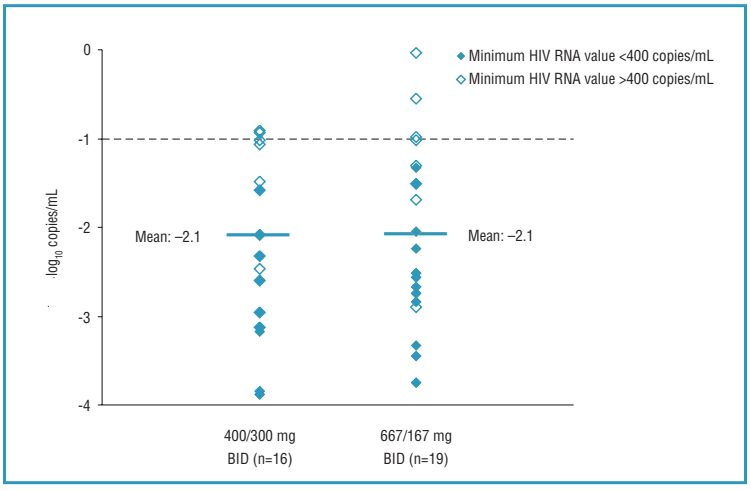


Figure 3. Maximum Change from Baseline in HIV RNA for Individual Patients



- No statistically significant differences were observed between treatment groups for the proportion of subjects with HIV RNA levels <50 copies/mL through Week 48 (Figure 4).
- At Week 48 by On-Treatment analysis, 3/6 patients (50%) in the 400/300 mg BID and 6/10 patients (60%) in the 667/167 mg BID group achieved HIV RNA <400 copies/mL.
- Mean increases from baseline in CD4 cell count were observed at all visits in each treatment group (Figure 5).

Figure 4. Proportion with HIV RNA <50 copies/mL

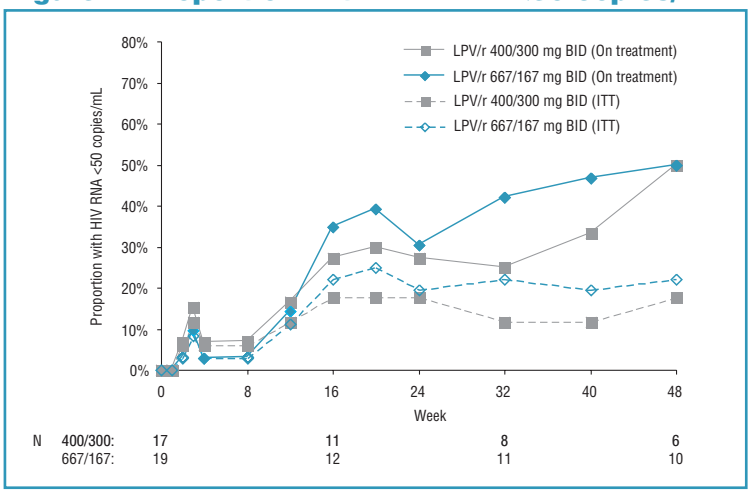
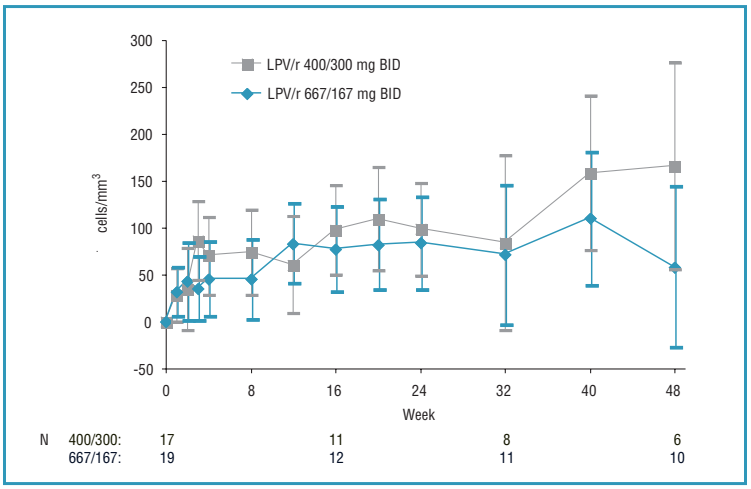


Figure 5. Mean Change from Baseline (95% CI) in CD4 Cell Count



Safety

- The most common adverse events were gastrointestinal in nature (Table 2).
- Study drug associated diarrhea, vomiting and dizziness of moderate or greater severity tended to occur more frequently in the 400/300 mg BID group compared to the 667/167 mg BID group.
- Among events of all severities or relationship to study drug, vomiting occurred significantly more frequently in the 400/300 mg group (35%) compared to the 667/167 group (5%, p=0.04).

Table 2. Moderate and Severe Treatment-Emergent Adverse Events of Possible, Probable, or Unknown Relationship to Study Drug – Incidence Through 48 Weeks

	Number (%) of Subjects	
Adverse Event	400 mg/300 mg BID (N=17)	667 mg/167 mg BID (N=19)
Diarrhea	4 (24%)	2 (11%)
Nausea	2 (12%)	3 (16%)
Asthenia	2 (12%)	1 (5%)
Dizziness	2 (12%)	0
Vomiting	2 (12%)	0

- Grade 3+ Lipid elevations were more common in the 400/300 mg BID group compared to the 667/167 mg BID group (Table 3), with a significant difference between groups in triglyceride elevations (p=0.02).
- Median changes from baseline to Week 48 in triglycerides and total cholesterol were +97 and +41 mg/dL, respectively, for the 400/300 mg BID group and -5 and -1 mg/dL, respectively, for the 667/167 mg BID group.
- In the 667/167 mg BID group, Grade 3+ lipid elevations were infrequent in patients without elevated lipids at baseline. Only 1 patient in the 667/167 mg BID group with values below grade 2 (≤240 mg/dL for cholesterol and ≤400 mg/dL for triglycerides) at baseline demonstrated a grade 3 value during the study (Table 4).

Table 3. Cumulative Grade 3/4 Laboratory Abnormalities Occurring in >2 Patients

	Number (%) of Subjects	
Variable (Grade 3 Criterion)	400 mg/300 mg BID (N=17)	667 mg/167 mg BID (N=19)
SGOT/AST (>5xULN)*	2 (12%)	3** (16%)
SGPT/ALT (>5xULN)*	2 (12%)	3** (16%)
Total Cholesterol (>300 mg/dL)	7 (41%)	5 (26%)
Triglycerides (>750 mg/dL)	11 (65%)	4 (21%)

* No symptomatic hepatitis was reported during the study. Only one subject who demonstrated a Grade 3+ SGOT/AST or SGPT/ALT had a measurement greater than Grade 2 at the final visit.
** One patient was HCV-antibody positive at baseline.

Table 4. Baseline and Maximum Total Cholesterol and Triglycerides Values

	Maximum Value Through Week 48 (Number of Subjects)							
	400/300 mg BID Treatment Group				667/167 mg BID Treatment Group			
Total Cholesterol (mg/dL)								
Baseline	≤240	>240-300	>300-400	>400	≤240	>240-300	>300-400	>400
≤240	6	4	1	1	11	3	1	0
>240-300	0	0	4	0	0	0	2	0
>300-400	0	0	0	1	0	0	0	2
Triglycerides (mg/dL)								
Baseline	≤400	>400-750	>750-1200	>1200	≤400	>400-750	>750-1200	>1200
≤400	3	2	5	3	8	5	1	0
>400-750	0	0	1	1	0	2	0	0
>750-1200	0	0	2	0	0	0	0	3

CONCLUSIONS

- Regimens based on LPV/r 400/300 mg BID and 667/167 mg BID demonstrate potent antiviral activity in this population with multiple prior regimen failures, with 83% of patients demonstrating a decrease in HIV RNA of at least 1.0 $\log_{10}$ copies/mL.
- While no significant efficacy differences between groups were observed, results suggested that the LPV/r 667/167 mg BID dose may be better tolerated, with fewer gastrointestinal events and lipid elevations compared to the LPV/r 400/300 mg BID dose.
- PK/PD analysis corroborated results of previous studies indicating the utility of the IQ as a predictor of virologic response.
- These data suggest higher doses of LPV/r may provide clinical benefit in patients with limited treatment options.

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