Poster #409W

Once-Daily vs. Twice-Daily Kaletra (lopinavir/ritonavir) in Antiretroviral-Naive HIV+ Patients: 48-Week Follow-up

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BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir, which functions as an inhibitor of cytochrome P450 3A. Even at low ritonavir doses, there is a substantial increase in LPV exposure. Lopinavir trough concentrations exceed the protein binding-adjusted IC_{50} of wild-type HIV by ≥75-fold when dosed at 400/100 mg twice a day,[1] potentially providing a barrier to emergence of viral resistance and activity against resistant virus.

Lopinavir/ritonavir (LPV/r, marketed as Kaletra™) has been studied in both antiretroviral-naive and experienced HIV-infected patients. The M99-056 study is an ongoing pilot study of LPV/r 800/200 mg QD or 400/100 mg BID both in combination with d4T (BID) and 3TC (BID) in antiretroviral-naive patients. This poster presents preliminary 48-week results on safety, efficacy and pharmacokinetics of these regimens.

METHODS

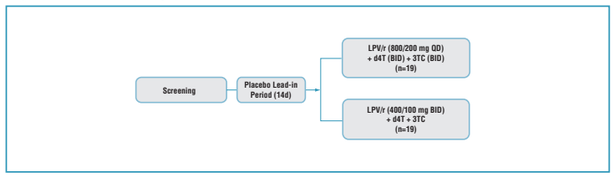
Entry Criteria

- Antiretroviral-naive patients
- Plasma HIV RNA level above 50 copies/mL
- No minimum CD4 cell count

Study Design and Analysis

- Thirty-eight antiretroviral-naive patients were randomized equally to receive LPV/r 800/200 mg QD or 400/100 mg BID. All patients also received d4T (30 mg or 40 mg BID) and 3TC (150 mg BID) (Figure 1).
- Patients started with a 14-day placebo lead-in period during which they were dispensed a supply of placebo capsules and were enrolled in a medication support and monitoring service. This was done to acclimate patients to daily use.

Figure 1. M99-056 Study Schema



- Steady-state plasma concentrations of LPV were measured throughout a dosing interval at Week 3.
- Additional LPV trough levels were measured at Weeks 8, 16, 24, and 48.
- Noncompartmental methods used to determine pharmacokinetic (PK) variables.
- ANOVA performed on log-transformed PK variables; linear mixed effects analysis performed on log-transformed trough concentrations over Weeks 3-48.
- Median trough and IQ for individual subject calculated as the median trough observations from Weeks 3-48.
- Plasma HIV RNA was quantified using the Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitive PCR assay (LLQ 50 copies mL) at each visit.
- Adherence was measured by the Medication Events Monitoring System (MEMS®, AARDEX, Inc.) caps on the LPV/r bottles.

Virologic Evaluation

- Samples from all patients with viral load VL ≥400 copies/mL at Week 24, 32, 40 or 48 while on the assigned regimen were submitted for genotypic and phenotypic analysis. Genotype (GeneSeq™) and phenotype (PhenoSense™) were performed by ViroLogic, Inc.
- Genotypic resistance to LPV was defined as the development of any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 82, 84 and 90) and confirmed by phenotypic analysis.

RESULTS

Table 1. Baseline Characteristics

	QD (N=19)	BID (N=19)
Gender (No. patients)		
Male	13	13
Female	6	6
Age (years)		
Mean (range)	42 (25-74)	35 (22-54)
Race (No. patients)		
Caucasian	6	5
Black	6	9
Hispanic	4	5
Asian/Pacific Islander	3	0
Baseline HIV RNA (log_{10} copies/mL)		
Mean/Median	4.6/4.6	4.7/4.7
Range	3.5-5.6	2.8-5.9
CD4 count (cells/µL)		
Mean/Median	265/259	252/269
Range	5-917	6-474

Table 2. Patient Disposition at Week 48

	QD	BID
Patients enrolled	19	19
Patients discontinuing before Week 48	1	3
Study drug-related adverse event	1	1
Withdrew consent	0	1
Noncompliance*	0	1

* Patient-discontinued at discretion of Investigator

Pharmacokinetic Data

- LPV AUC and C_{max} were similar for the QD and BID regimens.
- Across all patients, LPV C_{trough} did not differ over time from Weeks 3 to 48 (p=0.55).
- Overall median lopinavir C_{trough}/IC_{50} (protein binding-adjusted) was 40 (range 3.6-220) for QD and 84 (range 36-174) for BID regimens.
- Two patients on QD regimen had median LPV C_{trough}/IC_{50} <10.

Figure 2. M99-056 Lopinavir Mean (SD) Concentration-Time Profiles, Week 3

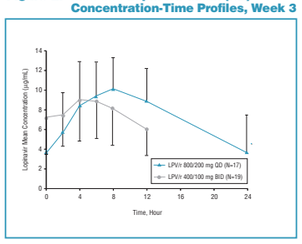


Figure 3. M99-056 Lopinavir Overall Median C_{trough} Scatter Plot

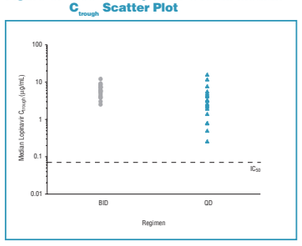
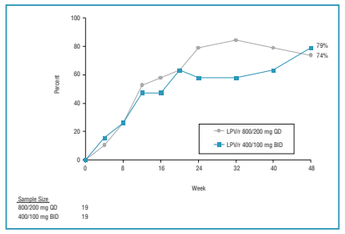


Table 3. Lopinavir Steady-State Pharmacokinetic and Pharmacodynamic Parameters

	800/200 mg QD (N=17)	400/100 mg BID (N=19)
Parameter	**Mean ± SD**	**Mean ± SD**
T_{max} (h)	6.6 ± 2.8*	4.4 ± 2.4
C_{max} (µg/mL)	10.94 ± 2.81	9.81 ± 3.66
C_{min} (µg/mL)	2.46 ± 2.63*	5.51 ± 2.68
C_{trough} (µg/mL)	3.62 ± 3.38*	7.13 ± 2.93
IQ (C_{trough}/IC_{50})*	40 (3.6-220)	84 (36-174)
AUC_{12} (µg•h/mL)	164.9 ± 67.5	185.2 ± 73.4[a]

* IQ is overall median (range) from Weeks 3-48; based on protein binding-corrected *wt*-HIV IC_{50}=0.07 µg/mL.
[a] Estimated as 2 x AUC_{12}. *Significantly different from BID (p<0.05, ANOVA.)

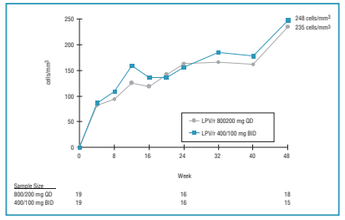
Figure 4. Proportion <50 Copies/mL (ITT M=F) at Week 48



Viral Load Suppression at 48 Weeks

- Intent-to-treat analysis (ITT M=F; missing values considered as treatment failure: 74% of patients and 79% of patients in the QD and BID groups, respectively, had VL <50 copies/mL at Week 48 (Figure 4).
- Of the five patients with HIV RNA levels above 50 copies/mL at Week 48, 2 had HIV RNA <100 copies/mL and all 5 had HIV RNA <1000 copies/mL.

Figure 5. Study 056 CD4 Cell Count Mean Change from Baseline



CD4 Response at 48 Weeks

- Among patients on study at Week 48, the mean CD4 cell count increases from baseline to Week 48 were 235 and 248 cells/mm³ for the QD and BID groups, respectively.

Genotype and Phenotype Results

- Genotypic and phenotypic results were available for 4 patients with viral load above 400 copies/mL between Week 24 and Week 48. Consistent with results observed in previous studies of LPV/r in ARV-naive patients,[2] 0 of 4 patients demonstrated resistance in protease, and 2 of 4 patients demonstrated resistance to lamivudine (M184V/I mutation).

Safety and Tolerability

- The most common study-drug related adverse events of at least moderate severity were diarrhea, nausea and asthenia, while the most common laboratory abnormality was lipid elevations (Table 3). Of note, lipid measurements were made without regard to fasting.
- One patient in the QD group prematurely discontinued on Day 4 due to pruritis, rash, chills, fever, nausea, vomiting, and diarrhea, all considered probably related to LPV/r. One patient in the BID group discontinued due to diarrhea and dehydration considered possibly related to LPV/r.
- One patient experienced an amylase elevation >2 times the upper limit of normal. Concurrent pancreatic amylase levels were within normal limits.
- Lipid elevations to Grade 3 levels were infrequent, occurring in 2 patients in each treatment group.
- Mean changes from baseline to Week 48 were similar between treatment groups for triglycerides (100 mg/dL in each group) and total cholesterol (42 mg/dL for the QD group and 53 mg/dL for the BID group).
- Fasting total cholesterol/HDL ratio at Week 24 was not significantly changed from baseline (-0.30 in QD and +0.01 in BID) treated patients.

Table 4. Most Common Adverse Events* and Grade 3/4 Laboratory Abnormalities

Event	QD (N=19)	BID (N=19)
Diarrhea	1	1
Nausea	3	1
Asthenia	0	2
Glucose (>250 mg/dL)	0	1
SGPT/ALT (>5 X ULN)	1	0
Total Cholesterol (>300 mg/dL)	1	1
Triglycerides (>750 mg/dL)	2	1
Amylase (>2 X ULN)	0	1

* Adverse events of at least moderate severity and probable, possible, or unknown relationship to LPV/r experienced by more than 1 patient is included.
** Laboratory determinations were performed without regard to fasting.

Adherence

- Dosing history for each patient was obtained using MEMS caps to monitor LPV/r dosing and provided to the clinical study sites.
- Adherence was similar between the treatment groups. The mean percentage of days with the correct number of LPV/r doses taken was 90% for the QD group and 87% for the BID group (p=0.88).

CONCLUSIONS

- Both LPV/r-based regimens exhibited a potent antiviral effect through 48 weeks in antiretroviral-naive patients, with VL<50 copies/mL by intent-to-treat (missing=failure) analysis with 74% and 79% of patients demonstrating VL <50 copies/mL in the QD and BID groups, respectively.
- LPV/r was well tolerated, with only two patients out of 38 discontinuing due to adverse events related to study drug prior to Week 48.
- Side effects were similar to those seen in other studies of LPV/r in ARV-naive patients.
- Overall median lopinavir C_{trough}/IC_{50} (protein binding-adjusted) was 40 (range 3.6-220) for QD and 84 (range 36-174) for BID regimens.
- A high rate of adherence was observed and was similar for the QD and BID groups, based on MEMS caps data. The tolerability profile and QD dosing of LPV/r may promote patient adherence, a critical factor in achieving long-term viral suppression.

ACKNOWLEDGMENTS

M99-056 Study Patients

AltaMed Health Services	M Lopez
Beth Israel Medical Center	G Costantini, A Murshak
Harbor UCLA Medical Center	M Guerrero
Infectious Diseases Physicians	J Gourley
Infectious Diseases Research Institute	K Halkias
Rush-Presbyterian-St. Luke's Medical Center	J Mohlman
Tower Infectious Diseases	T Clover
University of Cincinnati	P Daniel
University of North Carolina at Chapel Hill	D Ragan
Westchester Medical Center	K O'Keefe
Paragon Biomedical	J Ball, E Campbell, N Miyao
Abbott Laboratories	A Potthoff, R Heuser, K Robinson, C Foit, M Luo, C Locke, Y-L Chiu, X Ye

REFERENCES

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