Safety and Tolerability

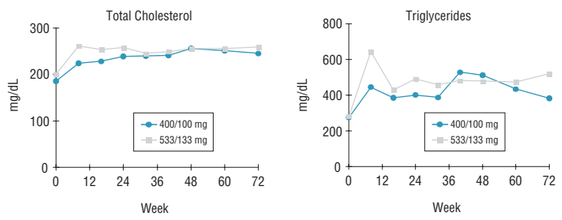
- The most common study drug-related adverse events of at least moderate severity were diarrhea and asthenia, while the most common laboratory abnormality was lipid elevations (Table 4). Results are expressed as the cumulative incidence over 72 weeks. Of note, lipid measurements were made without regard to fasting.
- Thirteen patients discontinued the study through 72 weeks; of these, 4 discontinuations were due to adverse events/laboratory abnormalities probably or possibly related to LPV/r in the opinion of the investigator.
- None of the patients who experienced amylase values >2 x ULN through Week 72 had associated elevations of pancreatic amylase (>2 x ULN).

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

Event	Percentage of Patients (n=57)
Diarrhea	12%
Asthenia	11%
Glucose (>250 mg/dL)	5%
SGOT/AST (>5 x ULN)	4%
SGPT/ALT (>5 x ULN)	4%
Total Cholesterol (>300 mg/dL)	40%
Triglycerides (>750 mg/dL)	40%
Amylase (>2 x ULN)	11%
Neutrophils (<0.75 x 10^9/L)	7%

*Adverse events of at least moderate severity and probable, possible, or unknown relationship to LPV/r included.

Figure 9. Mean Lipid Values Over Time



- There is a suggestion of greater lipid increases on the 533/133 mg dose compared to the 400/100 mg dose prior to the dose increase between Weeks 24 and 48 (Figure 9).
- Total cholesterol/HDL cholesterol ratios were obtained in a subset of fasting patients and did not significantly change from baseline through 24 weeks of LPV/r therapy (400/100 mg=+0.29, N=11, p=0.53; 533/133 mg=+0.48, N=13, p=0.26).

CONCLUSIONS

- LPV/r and EFV based therapy exhibits a potent antiviral effect through 72 weeks in multiple PI-experienced, NNRTI-naïve patients.
- Virologic response decreases incrementally as the number of baseline protease mutations increases and phenotype susceptibility to LPV decreases. A marked decrease in virologic response was observed with 8 or more baseline protease mutations or >40-fold reduced susceptibility to LPV.
- LPV/r should be increased to 533/133 mg BID when coadministered with EFV in patients where reduced susceptibility to LPV is suspected.
- LPV/r and EFV were well tolerated and associated with a low rate of discontinuation for treatment related adverse events through 72 weeks.

ACKNOWLEDGMENTS

Efavirenz was supplied by DuPont Pharmaceuticals Company. Phenotype testing of baseline viral isolates was performed by ViroLogic, Inc.

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Poster #1925

41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, December 2001

Kaletra (lopinavir/ritonavir) and Efavirenz: 72-Week Safety and Efficacy Evaluation in Multiple PI-Experienced Patients

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BACKGROUND

The M98-957 study is an ongoing phase II, open-label, randomized trial of Kaletra (lopinavir/ritonavir [LPV/r], formerly known as ABT-378/r), in combination with efavirenz, in multiple PI-experienced/NNRTI-naïve patients. Pharmacokinetic data and 72 week efficacy and safety data are reported here. Association of virologic response through Week 72 with baseline virologic genotype/phenotype is presented as well.

METHODS

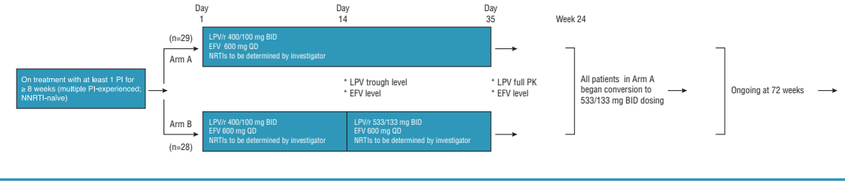
Entry Criteria

- HIV RNA >1,000 copies/mL on present PI regimen (no CD4 cell count restriction).
- On treatment with at least 1 PI for ≥ 8 weeks at study entry.
- Multiple PI-experienced (history of sequential or concurrent treatment with at least 2 PIs for at least 3 months each).
- NNRTI-naïve.

Study Design and Analysis

- 57 patients received LPV/r 400/100 mg (3 coformulated capsules) BID in place of their current PI, in combination with efavirenz (600 mg QD) and NRTIs as determined by the investigator, for the first 13 days of the study (Figure 1).
- On study Day 14, patients randomized to Arm B (n=28) increased their LPV/r dose to 533/133 mg (4 coformulated capsules) BID, while patients in Arm A (n=29) remained on the 400/100 mg BID dose (Figure 1).
- Lopinavir trough levels were drawn at Week 2; full PK was performed at Week 5; efavirenz levels were also drawn at Weeks 2 and 5.
- Plasma HIV RNA was quantified using the Roche Amplicor HIV-1 Monitor (assay lower limit of quantitation [LLQ] 400 copies/mL) and Roche Ultrasensitive assay (LLQ 50 copies/mL).
- All patients in Arm A began conversion to the 533/133 BID dose after Week 24 and completed the process prior to their Week 48 visit.

Figure 1. Study Design



- Efficacy/safety results presented for both dose groups combined (except lipid results).

RESULTS

Table 1. Baseline Characteristics

	All Patients (n=57)
Mean age, years	42
Men, %	79%
Race or ethnicity, %	
Caucasian	88%
Black	9%
Hispanic	7%
HIV RNA level (log_{10} copies/mL)	
Median (Range)	4.5 (2.6-6.4)

Pre-Study Antiretroviral Therapy

- Prior PI use included IDV (86%), RTV (77%), SQV (72%), and NFV (58%).
  - Mean number of prior PIs=3 (range: 1-4)
  - For patients who received RTV pre-study, 66% (29/44) received it as dual PI therapy.
- Prior NRTI use included ZDV (93%), 3TC (91%), d4T (91%), ddI (79%), ddC (46%), and ABC (18%).
  - Mean number NRTIs at baseline=2 (range: 1-4).
  - 75% of patients did not receive a new NRTI in conjunction with LPV/r and efavirenz within the first eight weeks of study.
- Mean number of prior ARVs=7 (range: 3-10).

Baseline Viral Susceptibility

- Protease inhibitor phenotypic susceptibility data were available for 56 of 57 baseline viral isolates (PhenoSense™,ViroLogic, Inc.).
- Sixty-eight percent (38/56) of patients had baseline viral isolates demonstrating cross resistance (≥4-fold increase in IC_{50} relative to wild-type virus) to at least 3 licensed PIs.
- Forty-three percent of patients had baseline viral isolates (24/56) demonstrating ≥10-fold increase in IC_{50} of lopinavir relative to wild-type virus.

Table 2. Baseline PI Phenotypic Susceptibility

	Median Fold Change in IC_{50} Relative to Wild-Type Virus (Range) All Patients
Lopinavir	5 (0.5 - 96)
Indinavir	10 (0.8 – 171)
Nelfinavir	20 (1.1 – 158)
Ritonavir	28 (0.5 – 316)
Saquinavir	6 (0.4 – 546)
Amprenavir	2 (0.5 – 49)

Pharmacokinetic Data

- Lopinavir levels achieved with the 400/100 mg dose are reduced when co-dosed with efavirenz (C_{trough} reduced ~33%; AUC reduced ~25%) based on comparison to historical data obtained in HIV patients who received LPV/r without efavirenz.
- LPV/r 533/133 mg dose with efavirenz provides similar lopinavir exposures to the 400/100 mg dose without efavirenz based on historical controls.[1]
- Efavirenz levels are similar for both LPV/r dose levels studied.

Table 3. Patient Disposition at Week 72

Patients Enrolled	57
Patients Discontinued at or Before Week 72	13
Discontinuations Related to LPV/r*	
CNS sx	2
Lactic Acidosis	1
Hyperlipidemia	1**
Other Reasons for Discontinuation	
Adverse Events (CNS sx, hypertriglyceridemia)	2
Virologic Failure	5**
Personal Reasons	1
Death (Septic Shock)	1
Patient Required Prohibited Medication***	1

* Adverse events noted as probably or possibly related to LPV/r are included.
** One patient discontinued for both hyperlipidemia and virologic failure.
*** Enrolled in an experimental IL-2 clinical trial.

Viral Suppression at 72 Weeks

- Intent-to-treat analysis (ITT M=F; missing values [M] considered as treatment failure [F]): 67% of patients had VL <400 copies/mL and 61% had VL <50 copies/mL at Week 72 (Figures 2 and 3).
- On-treatment analysis (OT): 88% of patients had viral load (VL) <400 copies/mL and 81% had VL <50 copies/mL at Week 72 (Figures 2 and 3).

Figure 2. Proportion <400 copies/mL at Week 72

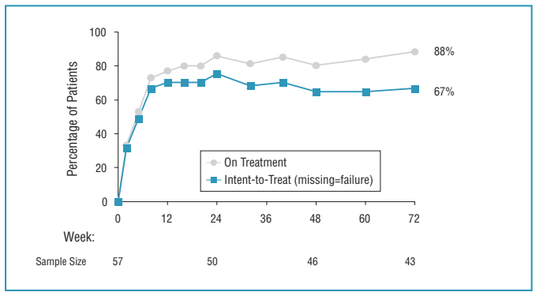
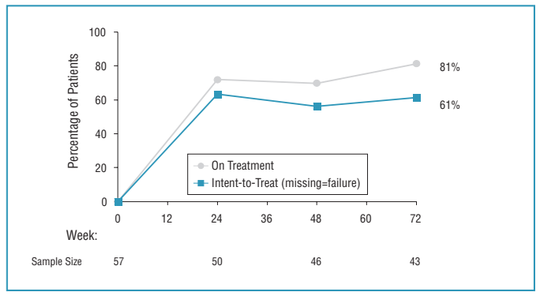
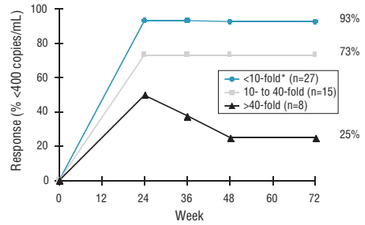


Figure 3. Proportion <50 copies/mL at Week 72



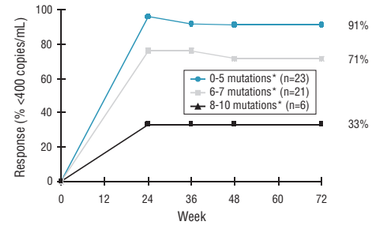
Association of Week 72 Virologic Response with Baseline Virologic Genotype/Phenotype

Figure 4. Virologic Response (<400 copies/mL) with Respect to Baseline Phenotype



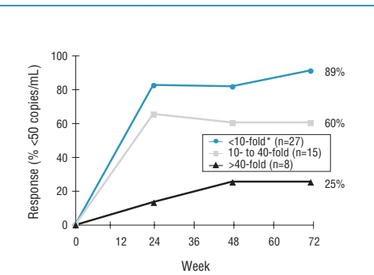
* Baseline LPV Phenotype (Fold IC_{50})

Figure 5. Virologic Response (<400 copies/mL) with Respect to Baseline Genotype



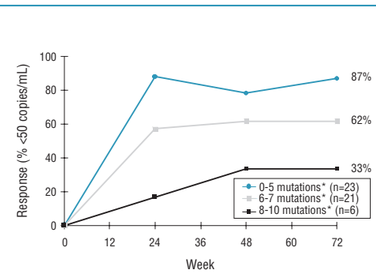
* Selected from 11 mutations associated with reduced susceptibility to LPV (protease/amino acid positions 10, 20, 24, 46, 53, 54, 63, 71, 82, 84, and 90)

Figure 6. Virologic Response (<50 copies/mL) with Respect to Baseline Phenotype



* Baseline LPV Phenotype (Fold IC_{50})

Figure 7. Virologic Response (<50 copies/mL) with Respect to Baseline Genotype



* Selected from 11 mutations associated with reduced susceptibility to LPV (protease/amino acid positions 10, 20, 24, 46, 53, 54, 63, 71, 82, 84 and 90)

- At 72 weeks, a high response rate at <400 copies/mL (93%) and <50 copies/mL (89%) was observed in patients whose baseline isolates displayed <10-fold reduced *in vitro* susceptibility to lopinavir at baseline (Figures 4 and 6). Response rates diminished incrementally in patients with 10-40 and >40-fold reduced susceptibility to lopinavir at baseline.
- Similarly, a high response rate at 72 weeks at <400 copies/mL (91%) and <50 copies/mL (87%) was observed in patients whose baseline isolates contained 0-5 protease mutations associated with reduced *in vitro* susceptibility to lopinavir (Figures 5 and 7). Response rates diminished incrementally in patients with a baseline lopinavir mutation score of 6-7 and 8-10.

CD4 Response at 72 Weeks

- Among patients on study at Week 72, the mean CD4 cell count was 431 cells/mm³ (mean change from baseline of 126 cells/mm³) (Figure 8). No significant differences between treatment groups were observed after Week 2.

Figure 8. Mean Change from Baseline in CD4 Cell Count