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Safety and Efficacy of Lopinavir/Ritonavir in Women in a Phase III Study of Antiretroviral-Naïve Subjects

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BACKGROUND

Lopinavir/ritonavir (LPV/r) is a novel protease inhibitor (PI) that achieves lopinavir trough concentrations >75-fold above the IC_{50} of LPV relative to wild type virus when dosed at 400/100 mg BID.

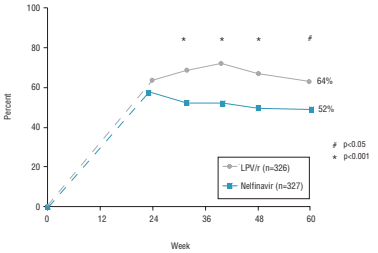
M98-863 was a double-blind, randomized trial comparing the safety and antiviral activity of LPV/r+d4T+3TC to that of nelfinavir (NFV)+d4T+3TC in antiretroviral-naïve patients. It was conducted at 93 centers in 13 countries, covering 5 continents and was one of the largest prospective, randomized clinical trials of PI therapy.

A statistically significantly greater proportion ofLPV/r-treated patients vs. NFV-treated patients had viral load <50 copies/mL at all visits after Week 24 through Week 60 (Figure 1).[1]

Among patients with detectable viral load and available genotype between Week 24 and Week 60, protease inhibitor resistance was not observed in viral isolates from any LPV/r-treated patients. In contrast, isolates from 37% of NFV-treated patients with detectable viral load demonstrated protease resistance. Resistance to 3TC was observed significantly more frequently in NFV-treated compared to LPV/r-treated patients (82% vs. 38%, p<0.001).[2]

Given the increasing prevalence of HIV infection in women, this subanalysis was performed to assess the efficacy and safety profile of LPV/r in men and women.[3]

Figure 1. Proportion of Patients with Viral Load <50 Copies/mL (ITT NC=F)



METHODS

Entry Criteria

- Age ≥12 years
- HIV positive with an HIV RNA level >400 copies/mL by the Roche Amplicor assay
- No CD4 cell count restriction
- No prior d4T or 3TC use
- No more than 14 days of any other antiretroviral therapy

Study Design

- In this randomized double-blind clinical trial, 653 antiretroviral-naïve patients received either LPV/r BID and NFV placebo TID plus d4T and 3TC (n=326) or NFV TID and LPV/r placebo BID plus d4T and 3TC (n=327). Patients were allowed to switch their nelfinavir or nelfinavir placebo dosing from TID to BID after the FDA approval of BID dosing and local IRB/IEC approval. Patients were unblinded after Week 60.

Analytical Methods

- All analyses in this poster were performed on the first 60 weeks of data since all patients were blinded through that time point. Female and male LPV/r-treated patients were compared in these analyses.
- The proportion of patients with HIV RNA <50 copies/mL at each visit was analyzed using an intent-to-treat (noncompleter=failure) method, in which missing values were considered failures unless the immediately preceding and immediately following HIV RNA levels were <50 copies/mL, and an on-treatment method, in which missing values were excluded from the analysis.
- For the Time to Loss of Virologic Response analysis, loss of virologic response was defined as the first of two consecutive viral load measurements above 400 copies/mL following any value <400 copies/mL. If the final viral load available was the first rebound above 400 copies/mL, the patient was considered a virologic failure at that point. Patients who never achieved viral load <400 copies/mL were considered virologic failures on day 1. Kaplan-Meier estimates of the time to loss of virologic response were computed, and the groups were compared using the Cox proportional hazards model.

RESULTS: COMPARISON OF LPV/R-TREATED PATIENTS

Baseline Characteristics and Disposition

- Time to loss of virologic response through Week 60 was similar between female and male LPV/r-treated patients (Week 60 response: 83% for female patients and 85% for male patients, Figure 4).

RESULTS: COMPARISON OF LPV/R-TREATED PATIENTS

Baseline Characteristics and Disposition

- Female patients receiving LPV/r were less likely to be Caucasian and had lower weight compared to male patients receiving LPV/r. Mean age and time since diagnosis were similar (Table 1).
- The rate of premature study discontinuation through Week 60 was comparable among female (26%) and male (21%) patients receiving LPV/r-based therapy (Table 2).
- Of note, discontinuations due to study drug-related adverse events and virologic failure were infrequent.

Table 1. Demographic Characteristics

	Female (N=66)	Male (N=260)	p-value
Age (years)			
Mean (Range)	41 (21-65)	38 (19-84)	NS
Race			
Caucasian	33%	62%	<0.001
Black	50%	18%	
Hispanic	15%	15%	
Other	2%	5%	
Weight (kg)			
Mean (Range)	68 (39-136)	75 (43-120)	<0.001
Time since diagnosis (years)			
Mean (Range)	1.9 (0.1-13.5)	2.3 (0-15.5)	NS

Table 2. Patient Disposition at Week 60 for LPV/r Patients

	Female	Male
Patients enrolled	66	260
Patients discontinuing by Week 60*	17 (26%)	54 (21%)
Death	1 (2%)	5 (2%)
Study Drug-Related Adverse Event	5 (8%)	7 (3%)
Other AE/HIV-Related Event	2 (3%)	9 (3%)
Virologic Failure	0 (0%)	2 (1%)
Lost to Follow-up	4 (6%)	12 (5%)
Noncompliance	1 (2%)	8 (3%)
Required Prohibited Medication	0 (0%)	1 (<1%)
Personal Reasons/Other	5 (8%)	14 (5%)

* Patients could indicate more than one reason for discontinuation.

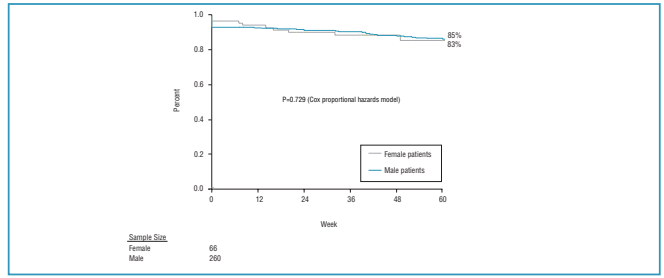
Efficacy

- Similar virologic response was observed, as indicated by the proportions of LPV/r-treated female and male patients with HIV RNA<50 copies/mL at Week 60 in an intent-to-treat (noncompleter=failure) analysis (61% vs. 65%, respectively, Figure 2) and an on-treatment analysis (82% in each group, respectively, Figure 3).

Figure 2. Proportion of LPV/r Patients with Viral Load <50 Copies/mL (ITT NC=F)

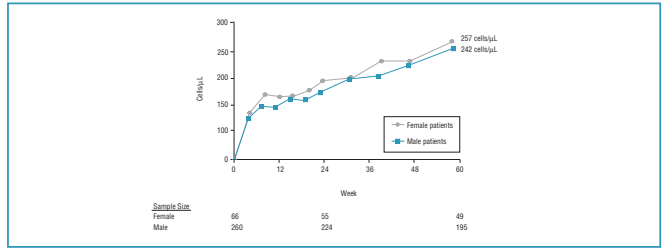
- Time to loss of virologic response through Week 60 was similar between female and male LPV/r-treated patients (Week 60 response: 83% for female patients and 85% for male patients, Figure 4).

Figure 4. Kaplan-Meier Estimates of the Time to Loss of Virologic Response for LPV/r Patients



- Immunologic response, as measured by the mean change from baseline to Week 60 in CD_4 cell count, was similar between female (+257 cells/μL) and male (+242 cells/μL) patients receiving LPV/r (Figure 5).

Figure 5. CD_4 Cell Count Mean Change from Baseline for LPV/r Patients



Lack of Resistance

- No LPV/r-treated patient (0/10 female patients and 0/41 male patients) with HIV RNA >400 copies/mL and available genotype between Week 24 and Week 60 developed protease inhibitor resistance, as defined by the development of mutations at amino acid positions (8, 30, 32, 46, 47, 48, 50, 82, 84, and 90)[a] in protease.
- Two of 10 (20%) female LPV/r-treated patients with genotype available developed resistance to 3TC compared with 17/41 (41%) male patients. The difference between the two groups was not statistically significant.

Safety

- Moderate or severe nausea and dyspepsia of probable or possible relationship to LPV/r occurred significantly more frequently in female vs. male patients through Week 60 (Table 3), although they did not result in significant differences in interruption or discontinuation.
- This observed higher rate of nausea in female patients does not appear to be related to lower body weight, since higher weight was associated with higher nausea incidence after adjusting for gender and race in a multiple logistic regression model.
- Moderate or severe nausea led to interruption or discontinuation of LPV/r in 1 and 0 female patients, respectively. The patient with temporary interruption remained on study for over 2 years with undetectable HIV RNA following rechallenge.

Figure 2. Proportion of LPV/r Patients with Viral Load <50 Copies/mL (ITT NC=F)

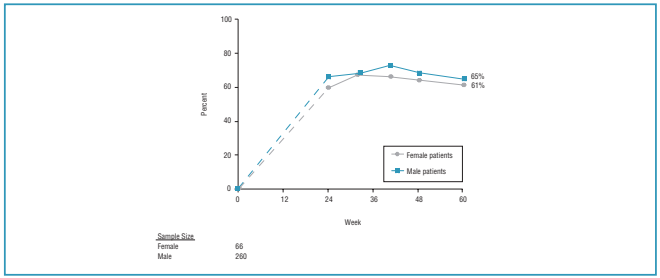


Figure 3. Proportion of LPV/r Patients with Viral Load <50 Copies/mL (OT)

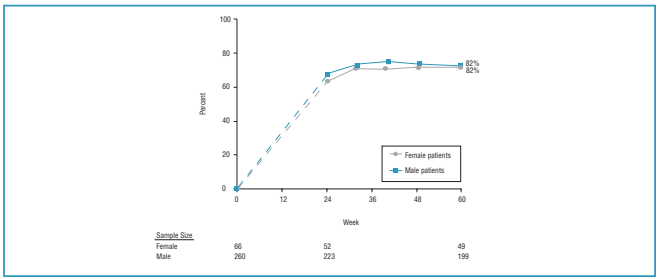


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Table 3. Most Common Adverse Events* Through Week 60

	Female (N=66)	Male (N=260)	p-value
Abdominal Pain	3%	4%	NS
Asthenia	2%	5%	NS
Headache	0%	3%	NS
Diarrhea	11%	18%	NS
Dyspepsia	8%	2%	0.032
Nausea	14%	6%	0.037
Vomiting	6%	2%	NS
Acne	3%	1%	NS

* Events of moderate or greater severity with a possible or probable relationship to study drug are included.

- Female LPV/r-treated patients had a significantly lower incidence of Grade 3/4 triglyceride elevations through Week 60 than male patients (Table 4), consistent with previous reports of gender differences in triglyceride increases, particularly in d4T-containing regimens.[5]
- Male patients had significantly higher mean baseline triglyceride values compared to female patients (171 vs. 141 mg/dL, p=0.028), and both gender and baseline triglyceride levels were significantly associated with Grade 3/4 elevations in a multiple logistic regression model.

Table 4. Grade 3/4 Laboratory Abnormalities* Through Week 60

	Female	Male	p-value
Amylase (>2 x ULN)	3%	4%	NS
SGOT/AST (>5 x ULN)	6%	2%	NS
SGPT/ALT (>5 x ULN)	5%	5%	NS
Glucose (>13.75 mmol/L or >250 mg/dL)	2%	2%	NS
Total Cholesterol (>7.77 mmol/L or >300 mg/dL)	6%	12%	NS
Triglycerides (>8.25 mmol/L or >750 mg/dL)	2%	13%	0.006

* Labs were drawn without regard to fasting.

CONCLUSIONS

- Efficacy was similar among female and male LPV/r-treated subjects.
- While differences in rates of certain adverse events and laboratory abnormalities were noted, overall safety and tolerability were comparable between female and male LPV/r-treated patients.

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ACKNOWLEDGMENTS

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