Abstract PL3.2

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Phase 3 Comparison of Lopinavir/ritonavir vs. Investigator-Selected Protease Inhibitors in Single PI-Experienced, NNRTI-Naive Patients: 48-Week Results of Study M98-888

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BACKGROUND

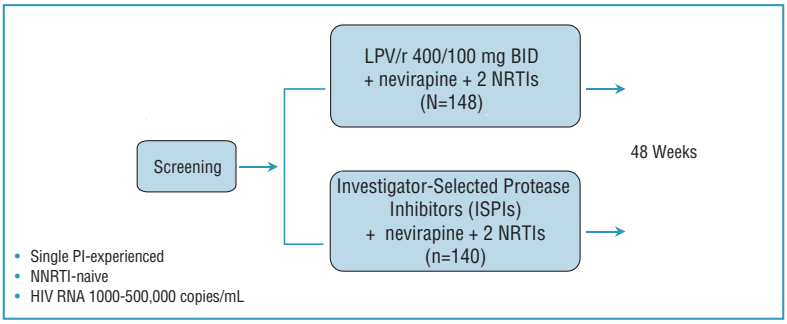
Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir, which functions as an inhibitor of cytochrome P450 3A. Even at low ritonavir doses, there is a substantial increase in LPV exposure.

The phase 2 development program for lopinavir/ritonavir (LPV/r) demonstrated antiviral activity and safety in a range of antiretroviral-naive[1], single PI-experienced[2], and multiple PI-experienced[3] patients. The current analysis presents the 48-week results of a phase 3 study initiated in 1999 and designed to confirm safety/efficacy of LPV/r in single PI-experienced, NNRTI-naive patients.

METHODS

- 288 single PI-experienced, NNRTI-naive patients experiencing virologic failure (HIV RNA >1000 copies/mL) on their current regimen were enrolled (Figure 1).
- Prior to randomization, the investigator selected a protease inhibitor regimen based on treatment history. Based on pharmacokinetic, safety, and efficacy data available at the time, allowed regimens included
  - Any single PI (NFV, IDV, RTV, SQV)
  - Select dual-PI regimens
    - RTV/SQV (400/400 mg BID)
    - RTV/IDV (400/400 mg BID)
    - NFV/SQV (1250/1200 mg BID or 750/800 mg TID)
- All patients also received nevirapine and 2 NRTIs.
- Virologic response was defined by FDA time to loss of virologic response algorithm (TLOVR), in which patients are responders if they achieve and maintain confirmed virologic response through 48 weeks. Patients who discontinue or demonstrate confirmed viral rebound are considered non-responders.

Figure 1. Study 888 Design



RESULTS

Baseline Characteristics

- Baseline characteristics were well-matched between treatment groups (Table 1).

Table 1. Study 888: Baseline Characteristics

	LPV/r (N=148)	ISPI(s) (N=140)
Gender		
Male	125 (84%)	124 (89%)
Female	23 (16%)	16 (11%)
Age (years)		
Mean (Range)	40 (18–73)	40 (25–71)
Race		
Caucasian	67%	67%
Black	20%	16%
Hispanic	11%	15%
Other	2%	2%
Baseline HIV RNA (log_{10} copies/mL)		
Mean	4.1	4.1
Range	2.6–5.8	2.6 – 6.0
CD4 count (cells/μL)		
Mean	313	331
Range	22–1059	10–1017

- The most common pre-study protease inhibitors were nelfinavir and indinavir (Figure 2).
- About 55% of patients had been exposed to dual-NRTI therapy or NRTI monotherapy prior to their pre-study PI-based regimen.
- The most common PI regimen used in the control arm during the study was saquinavir/ritonavir (400/400 mg BID) (Table 2).

Figure 2. Study 888: Pre-study Protease Inhibitors

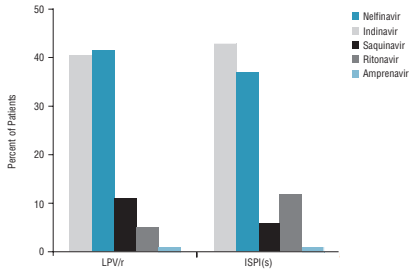


Table 2. Study 888: PI Use During Study

	LPV/r (N=148)	ISPI(s) (N=140)
Lopinavir/r	148 (100%)	
RTV/SQV		62 (44%)
RTV/IDV		29 (21%)
Nelfinavir		29 (21%)
Indinavir		8 (6%)
Other		12 (9%)

Disposition

- Premature discontinuation was significantly higher in the ISPI(s) group compared to the LPV/r group (Table 3), due to higher rates of virologic failure and discontinuation due to adverse events.

Table 3. Study 888: Subject Disposition at Week 48

	LPV/r	ISPI(s)	p-value
Enrolled	148	140	
Premature discontinuations	24%	43%	0.001
Death	1%	2%	NS
Study drug-related adverse event	5%	12%	0.032
Other adverse event	1%	1%	NS
Virologic failure	2%	13%	<0.001
Lost to follow-up	2%	5%	NS
Noncompliance	4%	4%	NS
Admission criteria violation	1%	0%	NS
Personal reasons/Other	9%	5%	NS

Efficacy

- Through 48 weeks, virologic response was significantly higher in the LPV/r group compared to the ISPI(s) group (57% vs. 33%, p<0.001, Figure 3).
- Among patients remaining on study, CD4 cell count increases were similar through 48 weeks (Figure 4).

Figure 3. Study 888: Proportion <400 Copies/mL Through Week 48: FDA TLOVR Algorithm (intent-to-treat)

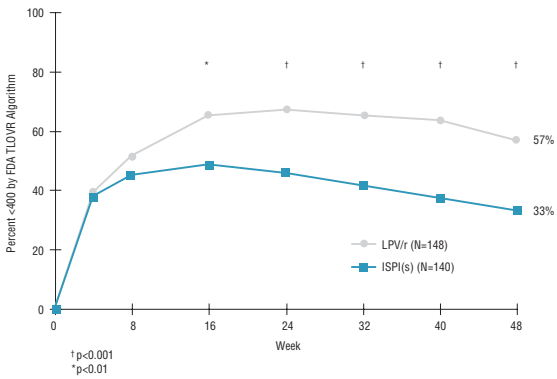
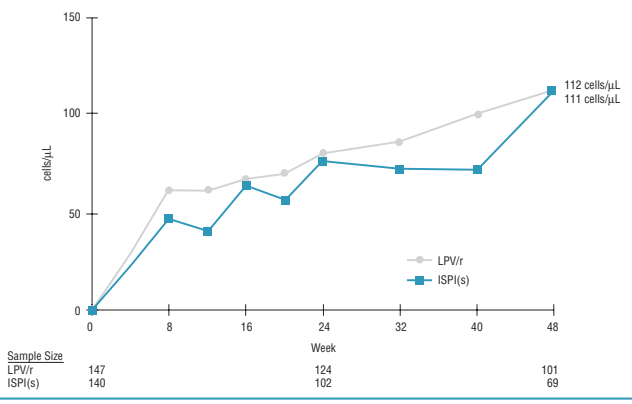


Figure 4. Study 888: Mean Change from Baseline in CD4 Cell Count



Safety

- With the exception of higher rates of nausea and vomiting in the ISPI(s) group, incidence of adverse events and grade 3+ laboratory abnormalities were similar between treatment groups (Table 4).

Table 4. Study 888: Most Common Adverse Events* and Grade 3/4 Lab Abnormalities

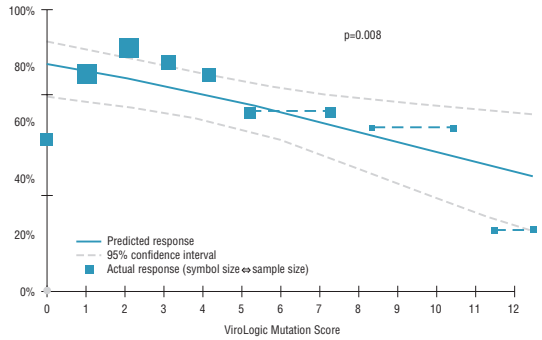
	LPV/r (N=148)	ISPI(s) (N=140)	p-value
Diarrhea	7%	9%	NS
Nausea	7%	16%	0.015
Vomiting	4%	12%	0.016
Asthenia	3%	6%	NS
SGOT/AST (>5 x ULN)	5%	11%	NS
SGPT/ALT (>5 x ULN)	6%	13%	NS
Total Cholesterol (>300 mg/dL)	20%	21%	NS
Triglycerides (>750 mg/dL)	25%	21%	NS

* Moderate/severe events of probable/possible relationship to PI

Resistance

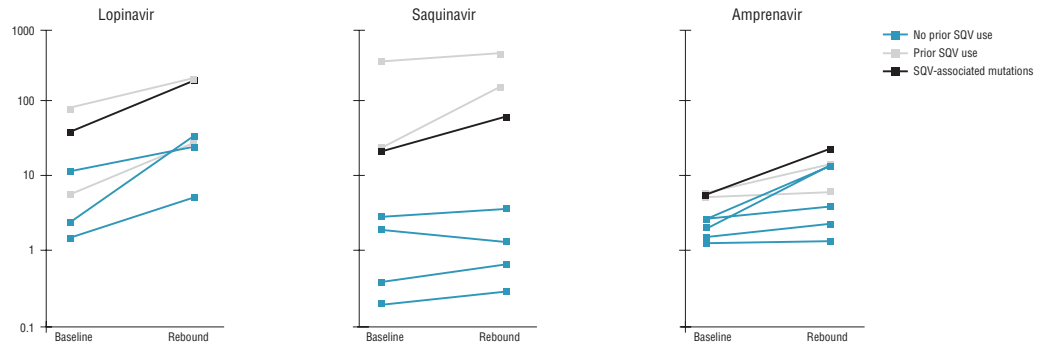
- In an assessment of six algorithms for predicting virologic response to LPV/r,[4] the ViroLogic algorithm[5] performed best, due to the 3-fold weights assigned to mutations at positions 54 and 82, which suggests a greater importance of mutations at these positions in predicting loss of virologic response (Figure 5).

Figure 5. Study 888: Virologic Response to LPV/r by ViroLogic Mutation Score



- 30 LPV/r-treated patients with HIV RNA >500 at Week 48 or final visit had samples submitted for resistance testing.
- Evolution of LPV resistance was defined as meeting 1 or both of the following: any new primary mutation in protease or any new secondary mutation + >2-fold change in LPV susceptibility compared to baseline.
- Nevirapine resistance was defined as mutations at amino acids 100, 101, 103, 106, 181, 188, 190 in reverse transcriptase.
- In 26 patients with results available, 7 (27%) demonstrated evolution of LPV resistance.
- 22/24 (92%) demonstrated NVP resistance (2 patients who discontinued NVP early in the study were excluded from the analysis of NVP resistance).
- Most patients with evolution of LPV resistance had virus that remained sensitive to SQV and/or APV, suggesting that a SQV/r-based or fosAPV/r-based regimen may be useful for salvage in the cases when additional LPV resistance develops (Figure 6).

Figure 6. Study 888: Limited Development of Cross-resistance to SQV and APV in 7 Patients with Evolution of LPV Resistance



RESULTS *continued*

Limitations

- The population studied in this trial (single PI-experienced, NNRTI-naive) is less common than when the trial was initiated due to the increasing use of NNRTI-based first-line regimens.
- While the control arm regimens were representative of the options then available, unboosted PIs are no longer commonly used in treatment-experienced patients, and the use of RTV 400 mg BID in dual-PI regimens is now atypical.
- While the limited diversity of baseline genotypes does not allow the assessment of the impact of protease mutations at positions 47 and 50 on virologic response to LPV/r, analysis confirmed that mutations at positions 54 and 82 appear to be somewhat more important in predicting response to LPV.

CONCLUSIONS

- The LPV/r-based regimen demonstrated superior antiviral activity compared to regimens based on investigator-selected PIs, in single PI-experienced, NNRTI-naive patients. 57% of LPV/r-treated patients achieved HIV RNA <400 copies/mL through 48 weeks (FDA TLOVR algorithm, intent-to-treat analysis) compared to 33% of patients treated with investigator-selected PIs.
- Gastrointestinal tolerability appeared somewhat better among LPV/r-treated patients
- Response to LPV/r was high in patients with fewer mutations at baseline. By ViroLogic mutation score:
  - Virologic response was >75% with a score of 1-4
  - Virologic response remained >55% with scores up to 10
  - I54 and V82 mutations were more important in predicting response to LPV/r
- Evolution of resistance to LPV was observed in 7/26 (27%) patients with resistance testing at rebound
  - Regimens based on ritonavir-boosted SQV or fosAPV may be useful in patients with evolution of LPV resistance
- NVP resistance in 22/24 (92%) patients with viral rebound during treatment with NVP

ACKNOWLEDGMENTS

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- Abbott Laboratories
  - B Bernstein, M Lindberg, G Yang, J Moseley, H Mo, D Kempf

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