Abstract P28

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Lopinavir/ritonavir (LPV/r)-Based Therapy in Antiretroviral (ARV)-Naïve, HIV-Infected Patients: 6-Year Follow-up of Study 720

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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. At a dosage of 400 mg of LPV/100 mg ritonavir twice daily (3 co-formulated capsules BID), ritonavir concentrations are below those required for antiviral activity.[1] By contrast, the mean LPV C_{trough}/IC_{50} ratio (Inhibitory Quotient or IQ) for wild-type HIV is ≥70 when dosed at 400/100 mg twice a day, potentially serving as a barrier to the emergence of drug resistance and providing activity against drug resistant virus.

Lopinavir/ritonavir (LPV/r, marketed as Kaletra™) has been studied in both antiretroviral-naïve and experienced HIV-infected patients. However, few long-term data are available on continued safety and efficacy. The M97-720 study is an ongoing phase II trial of LPV/r in combination with d4T and 3TC in antiretroviral-naïve patients. This was the first trial of LPV/r in HIV-infected patients and hence provides the longest duration of follow-up for patients treated with LPV/r. This poster presents data on antiviral activity, immunologic parameters, and safety through 6 years (312 weeks).

METHODS

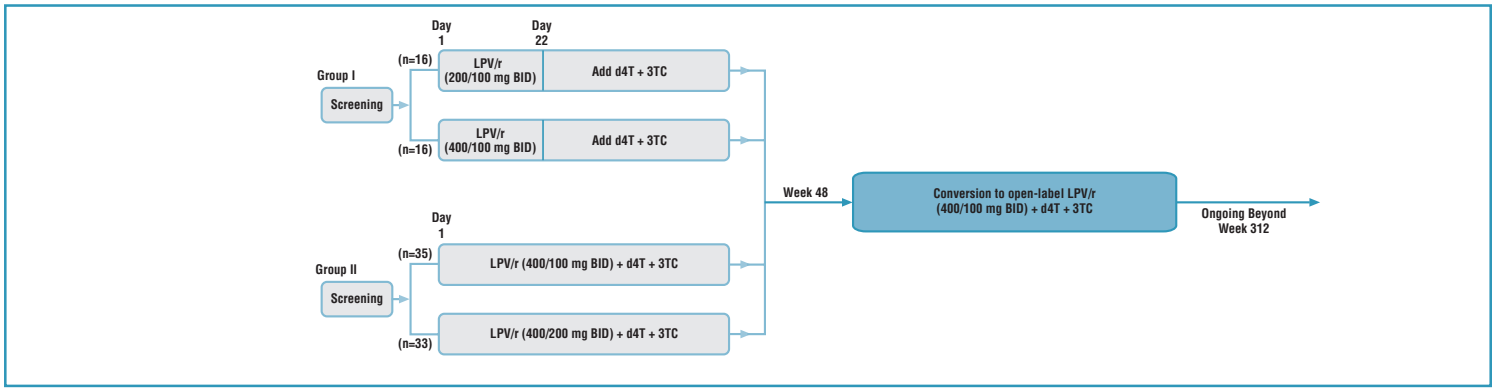
Entry Criteria

- Antiretroviral-naïve patients with confirmed HIV-1 infection.
- Plasma HIV RNA ≥5,000 copies/mL with no CD4 cell count restriction.
- Exclusion criteria included ALT or AST >2.5x Upper Limit Normal (ULN) and creatinine >1.5x ULN.

Study Design and Analysis

- One hundred antiretroviral-naïve patients were randomized to receive one of three dosage levels of LPV/r (200/100 mg BID, 400/100 mg BID or 400/200 mg BID), together with d4T (40 mg BID) and 3TC (150 mg BID) given either after 3 weeks of monotherapy (Group I) or from study entry (Group II) (Figure 1).
- Enrollment into Group II began following an evaluation of preliminary efficacy and safety of LPV/r in Group I.
- After 48 weeks, all patients converted to open-label LPV/r 400/100 mg BID dosing.
- Patients were evaluated every 2-4 weeks for the first 24 weeks and every 12 weeks thereafter.

Figure 1. M97-720 Study Schema



Efficacy

- Proportion of patients with HIV RNA below the limit of quantitation (LOQ) was measured using an on-treatment method (missing values and values obtained during treatment interruptions excluded) and an intent-to-treat, noncompleter=failure method (ITT NC=F, missing values considered failure unless the immediately preceding and following values were below the LOQ).
- Immunologic response was assessed by the mean change in CD4 count from baseline to each study visit.

Virologic Evaluation

- Samples from any patient with HIV RNA >500 copies/mL any time at or after Week 24 were submitted for genotypic and phenotypic analyses. Genotype (GeneSeq™) and phenotype (PhenoSense™) analyses 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, 54, 82, 84, and 90) confirmed by phenotypic analysis (≥2.5 fold increase in IC_{50} to LPV relative to wild type HIV). Resistance to 3TC was defined as the presence of an M184V and/or M184I mutation in reverse transcriptase.
- Resistance to stavudine (d4T) was defined as any thymidine analog mutation in reverse transcriptase (amino acids 41, 67, 70, 210, 215, 219).

METHODS *continued*

Safety

- Cumulative incidence through Week 312 for adverse events and grade 3/4 laboratory values was summarized, as was the prevalence at Week 312, defined as the presence of an ongoing adverse event or a grade 3/4 lab measurement obtained at the Week 312 visit.
- All laboratory measurements were obtained without regard to fasting.
- Events of fat distribution abnormalities/lipodystrophy were based on patient reports and investigator assessment of symptoms.

RESULTS

Efficacy

Viral Load Suppression Below the LOQ

- Based on the ITT NC=F analysis through Week 312, 63% of patients had HIV RNA <400 copies/mL (on-treatment analysis: 100%) (Figure 2) and 62% of patients had HIV RNA <50 copies/mL (on-treatment analysis: 98%) (Figure 3). One patient had HIV RNA between 50 and 400 copies/mL, but demonstrated resuppression to <50 copies/mL at subsequent visits.

Figure 2. Study 720: HIV RNA <400 copies/mL Through Week 312

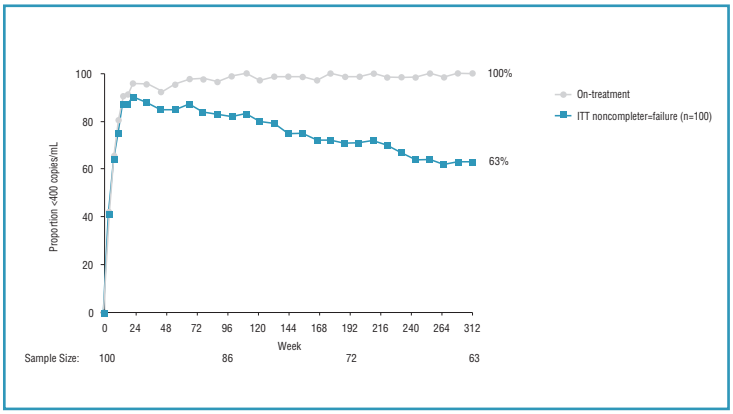
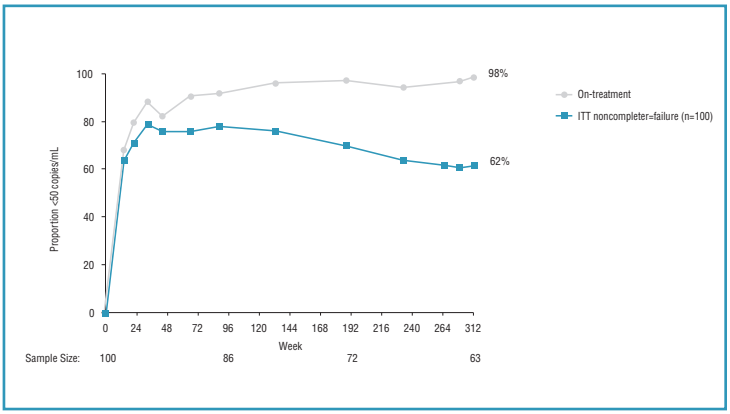


Figure 3. Study 720: HIV RNA <50 copies/mL Through Week 312



Analysis of Genotypic and Phenotypic Resistance

- A total of 33 samples from 28 patients were submitted for resistance testing (Figure 4).
- 17 patients met criteria for loss of virologic response, and 11 patients had at least 1 "blip" (single HIV RNA value >500 copies/mL bracketed by HIV RNA values <400 copies/mL) after Week 24.
- In 18 patients with available results, no lopinavir or stavudine resistance was observed, and 3 patients demonstrated lamivudine resistance. Correspondingly, no evidence of phenotypic resistance to any PI was observed (Figure 5).
- 6 patients demonstrated a substitution at a new position in protease during viral rebound (1 each at amino acids 15, 36, 43, 57, 63, 70). However, as demonstrated previously,[2] none of these substitutions are primary protease inhibitor mutations, no impact on PI phenotypic resistance was observed, and all 3 patients who remain on study demonstrated HIV RNA <50 copies/mL at the most recent visit.

Figure 4. Study 720: Virologic Disposition

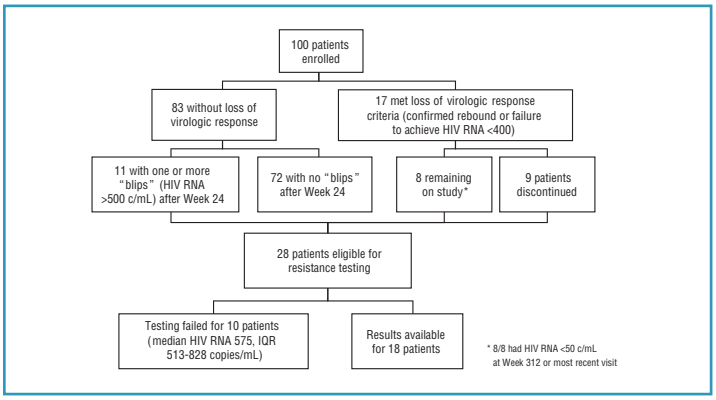
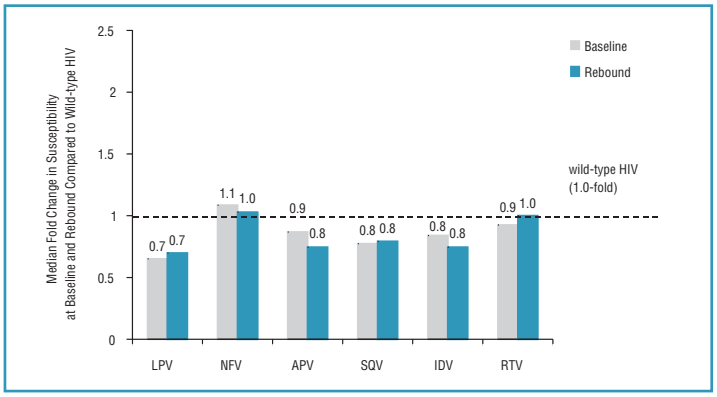


Figure 5. Study 720: PI Phenotypic Susceptibility at Baseline and Rebound



CD4 Cell Count Response

- Among subjects with values at both baseline and Week 312 (N=63), the mean CD4 cell count increased from 280 cells/mm^3 at baseline to 808 cells/mm^3 at Week 312, an increase of 529 cells/mm^3 (Figure 6).
- CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count (Table 1). Among patients with baseline CD4 cell count <50 cells/mm^3, mean CD4 cell count increased from 23 cells/mm^3 at baseline to 576 cells/mm^3 at Week 312, an increase of 553 cells/mm^3.

Figure 6. Study 720: Mean Change from Baseline in CD4 Count

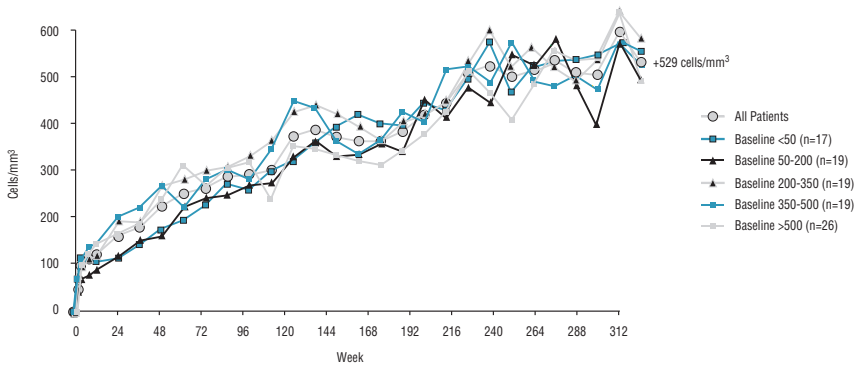


Table 1. CD4 Cell Count Increase at Week 312 by Baseline CD4 Cell Count

Baseline CD4 Cell Count in cells/mm^3 (Number of Patients with Values at Baseline and Week 312)	Mean CD4 Cell Count Increase from Baseline to Week 312 (cells/mm^3)
<50 (n=16)	553
50-199 (n=12)	491
200-349 (n=15)	581
350-499 (n=12)	521
≥500 (n=13)	490

Safety

Table 2. Patient Disposition Through Week 312

Patients enrolled	100
Discontinuations prior to Week 312	37
Discontinuations probably or possibly related to study drugs	
AST/ALT increases	2
Diarrhea	1
Liver pain, enlargement, fatty deposits	1
Arthralgia	1
Elevated lipids	2
Fat distribution abnormalities	5
Death[1]	1
Other reasons for discontinuation	
Adverse Event unrelated to study drugs (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification[2])	3
Lost to follow-up	9
Noncompliance	4
Personal/other reasons (moved (3), drug addiction, "virologic success"[3])	8
Patients on study at Week 312	63

[1] Death of unknown cause occurred in a patient 10 days following thoracic spinal surgery with perioperative myocardial infarction.

[2] One patient was discontinued due to both noncompliance and alcohol detoxification.

[3] One patient discontinued based on the primary physician's recommendation to temporarily suspend ARV treatment because the patient was "doing so well on present regimen."

Table 3. Most Common Adverse Events (occurring in ≥10% of patients) Through Week 312

Moderate/Severe Drug-related AEs	Incidence Through Week 312 (n=100)	Prevalence at Week 312 (n=63)
Diarrhea	28%	0%
Nausea	16%	0%
Lipodystrophy	13%	11%
Abdominal pain	10%	0%

Table 4. Most Common Grade 3/4 Laboratory Abnormalities (occurring in ≥10% of patients) Through Week 312

Grade 3/4 Lab Abnormalities	Incidence Through Week 312 (n=100)	Prevalence at Week 312 (n=63)
Cholesterol (>300 mg/dL)*	23%	5%
Triglycerides (>750 mg/dL)*	26%	6%
AST/ALT (>5X ULN)	11%	0%

*Taken without regard to fasting

Table 5. Distribution of Lipid Values at Week 312*

Category	Prevalence at Week 312 (n=63)	Prevalence at Week 312 or Last Available Value (n=100)
Total Cholesterol (mg/dL)		
<240	47 (75%)	71 (71%)
>240-300	13 (21%)	23 (23%)
300-400	3 (5%)	6 (6%)
>400	0	0
Triglycerides (mg/dL)		
<400	49 (78%)	79 (79%)
400-750	10 (16%)	15 (15%)
>750-1200	3 (5%)	4 (4%)
>1200	1 (2%)	2 (2%)

*Taken without regard to fasting
23 patients with grade 2 or higher lipid values initiated lipid-lowering agents, and all but 2 subsequently demonstrated grade 0-1 lipid values.

CONCLUSIONS

- Through 6 years (312 weeks) of follow-up, antiretroviral-naïve patients receiving LPV/r-based therapy exhibited sustained virologic responses, with 63% of patients demonstrating HIV RNA <400 copies/mL and 62% demonstrating HIV RNA <50 copies/mL by intent-to-treat (NC=F) analysis. Corresponding on-treatment response rates were 100% and 98%, respectively.
- Mean CD4 cell count increased 529 cells/mm^3 over 312 weeks of follow-up with consistent CD4 cell count increases regardless of baseline CD4 cell count.
- Through 312 weeks of follow-up, no primary protease inhibitor resistance mutations have been observed in subjects with HIV RNA >500 copies/mL any time at or after Week 24.
- LPV/r was well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (13/100, 13%).

ACKNOWLEDGMENTS

M97-720 Study Subjects
Covance Central Laboratory Services
AIDS Research Consortium of Atlanta *Moss J*
Beth Israel Deaconess Medical Center–Harvard *Fitch H*
Cornell Clinical Trials Unit *Stroberg T*
Duke University Medical Center *Harmon L*
Northwestern University *Bruce J*
Pacific Oaks Research *Simonson A*
Rush Presbyterian St. Luke's Medical Center *Fritsche J*
Thomas Street Clinic *Evans R*
University of Colorado *Putnam B, Basler C*
University of North Carolina at Chapel Hill *Marcus C*
PPD Development *Wheat R, Redd S*
Abbott Laboratories *Sheehan K, Yang G*

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2. Hicks C, da Silva B, King M, et al. Extensive Resistance Testing During 5 Years of Lopinavir/ritonavir Treatment in Antiretroviral-Naive HIV-Infected Patients: Results from Study 720. XV International AIDS Conference, Bangkok, Thailand, 2004 (WeOr-B1291).