Poster #225

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Kaletra (lopinavir/ritonavir) in Antiretroviral-Naive HIV+ Patients: 3-Year 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. At a dosage of 400 mg of LPV/100 mg ritonavir twice daily (3 co-formulated tablets 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 ≥75 when dosed at 400/100 mg twice a day, 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. However, few long-term data are available on continued safety and efficacy. The M97-720 study is an ongoing phase II double-blind trial of LPV/r in combination with d4T and 3TC in antiretroviral-naive 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 safety and efficacy through 156 weeks.

METHODS

Entry Criteria

- Antiretroviral-naïve patients.
- Plasma HIV RNA ≥5,000 copies/mL with no CD4 cell count restriction.

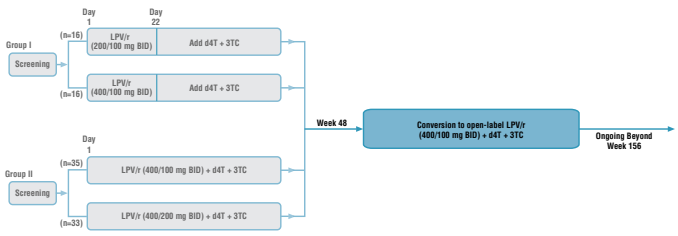
Study Design and Analysis

- 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 began conversion to open-label LPV/r 400/100 mg BID dosing.
- Plasma HIV RNA was quantified using Roche Amplicor HIV-1 Monitor™ (lower limit of quantitation [LLQ] 400 copies/mL) and the Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitative PCR, Version 1.0 (LLQ 50 copies/mL).

Antiviral Activity

- Proportion with HIV RNA below the LLQ (on treatment) at each visit: Patients who discontinued prior to the visit, patients with missing values, and values obtained during a treatment interruption of at least 3 days were excluded from the analysis.
- Proportion with HIV RNA below the LLQ (intent-to-treat [noncompleter=failure]) (ITT NC=F) at each visit: Patients who discontinued prior to the visit were considered non-responders (HIV RNA > LLQ). Patients with missing values at a visit were considered non-responders unless HIV RNA was below the LLQ at the immediately preceding and immediately following visits.
- Duration of virologic response was defined as the time from study initiation to the time of loss of virologic response (two consecutive HIV RNA measurements above 400 copies/mL following any measurement below 400 copies/mL). If the final measurement for a patient was above 400 copies/mL (and the patient had not previously demonstrated a loss of response), the time of loss of response was defined to be the time of the last measurement. Patients who had never experienced a loss of response were considered censored at the time of their final measurement, including patients who prematurely discontinued prior to demonstrating a loss of response. Patients who never achieved an HIV RNA level below 400 copies/mL were considered to have had a loss of response at Day 1.

Figure 1. M97-720 Study Schema



RESULTS

Baseline Characteristics

- Ninety-six male and 4 female patients: 65% Caucasian, 29% Black, 6% Hispanic.
- Mean age: 35 years (range 21-59).
- Median Plasma HIV RNA: 4.8 $\log_{10}$ copies/mL (range 3.3-6.3).
- Median CD4 count: 326 cells/mm³ (range 3-918).

Viral Load Suppression Below the LLQ

- Based on the ITT NC=F analysis, 75% of patients had HIV RNA <400 copies/mL at Week 156 (on-treatment analysis: 99%) (Figure 2).
- Based on the ITT NC=F analysis, 76% of patients had HIV RNA <50 copies/mL at Week 144 (on-treatment analysis: 96%) (Figure 3).

Figure 2. HIV RNA <400 copies/mL Through Week 156

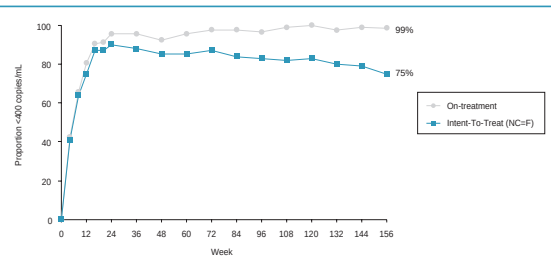
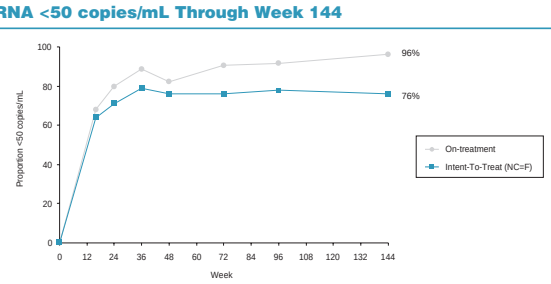


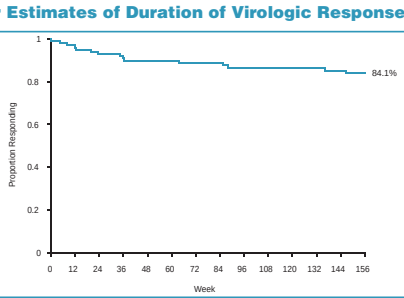
Figure 3. HIV RNA <50 copies/mL Through Week 144



Duration of Virologic Response Analysis

- Through Week 156, the Kaplan-Meier estimate of the proportion of patients maintaining virologic response was 84.1% (Figure 4).
- 8/15 patients (53%) who experienced loss of virologic response through Week 156 demonstrated resuppression of HIV RNA levels to <400 copies/mL at Week 156 or latest available study visit without change in ARV regimen.

Figure 4. Kaplan-Meier Estimates of Duration of Virologic Response



CD4 Cell Count Response

- Among subjects with values at both baseline and Week 156, the mean CD4 cell count increased from 298 cells/mm³ to 654 cells/mm³, an increase of 356 cells/mm³ (Figure 5).
- CD4 cell count response appeared to be consistent regardless of baseline CD4 cell count. Among 17 patients with baseline CD4 cell count ≤50 cells/mm³, mean CD4 cell count increased from 24 cells/mm³ to 438 cells/mm³, an increase of 414 cells/mm³.

Figure 5. CD4 Cell Count (Mean Change from Baseline)

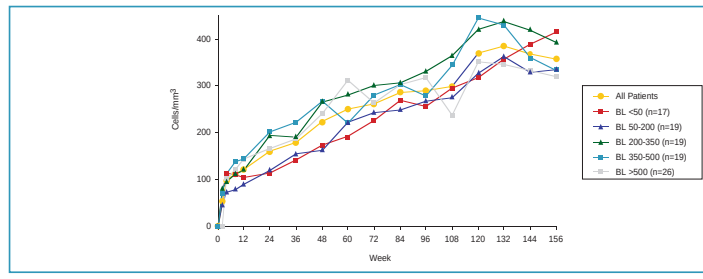


Table 1. Week 156 Safety Summary

Most Common Adverse Events* and Grade 3/4 Laboratory Abnormalities	All Patients (n=100)
Diarrhea*	25%
Nausea	16%
Abdominal Pain	9%
Abnormal Stools**	8%
Asthenia	8%
Headache	8%
Vomiting	6%
Cholesterol (>300 mg/dL)	17%
Triglycerides (>750 mg/dL)	16%
AST/ALT (>5X ULN)	10%

* Adverse events of at least moderate severity and probable, possible, or unknown relationship to LPV/r are included.
* >3 loose stools/day.
** ≤3 loose stools/day.

Table 2. Patient Disposition at Week 156

Patients enrolled	**100**
Patients discontinuing at or before Week 156	**23**
Discontinuations possibly or probably related to study drugs	
AST/ALT increases[1]	2
Diarrhea	1
Arthralgia	1
Death[2]	1
Other reasons for discontinuation	
Adverse event/HIV-related event unrelated to study drugs (lymphoma, hyperglycemia in diabetic patient, alcohol detoxification)	3
Personal reasons (left USA, drug addiction, moved out of state [2])	4
Noncompliance	4
Lost to follow-up	7

[1] Includes one patient with chronic hepatitis B infection at Baseline and another patient with Grade 2 elevations (2-5 times upper limit of normal), both asymptomatic.
[2] Death of unknown cause occurred in a patient ten days following thoracic spinal surgery with perioperative myocardial infarction.

Virologic and Immunologic Response with Respect to Current HIV Treatment Guidelines

- In January 2000 (prior to US regulatory approval of LPV/r), the International AIDS Society (IAS) issued guidelines[2] recommending initiation of ARV treatment in therapy-naive HIV-infected patients with CD4 cell count <350 cells/mm³ or viral load above 30,000 copies/mL. In August 2001, the U.S. Department of Health and Human Services (DHHS) issued updated guidelines[3] for the use of ARV therapy in adults and adolescents, recommending initiation of ARV treatment in therapy-naive HIV-infected patients with CD4 cell count <200 cells/mm³ or viral load above 55,000 copies/mL by RT/PCR. In July 2001, the British HIV Association (BHIVA) issued guidelines[4] recommending initiation of ARV treatment in therapy-naive HIV-infected patients with CD4 cell count <200 cells/mm³.
- In the DHHS guidelines, LPV/r is included in the "Strongly Recommended" category of agents to consider for initial treatment of established HIV infection.[3] The BHIVA guidelines also list LPV/r as an option for initial treatment of HIV infection.[4]
- At baseline in study M97-720, 79/100 (79%), 65/100 (65%) and 37/100 (37%) patients met the above IAS, DHHS and BHIVA criteria recommending ARV therapy initiation, respectively. Virologic and immunologic response among these patients (Figures 6 and 7) compare favorably to results from all patients reported above.

Figure 6. HIV RNA <400 copies/mL (ITT NC=F) — Patients Meeting Treatment Initiation Guidelines for ARV Therapy at Baseline

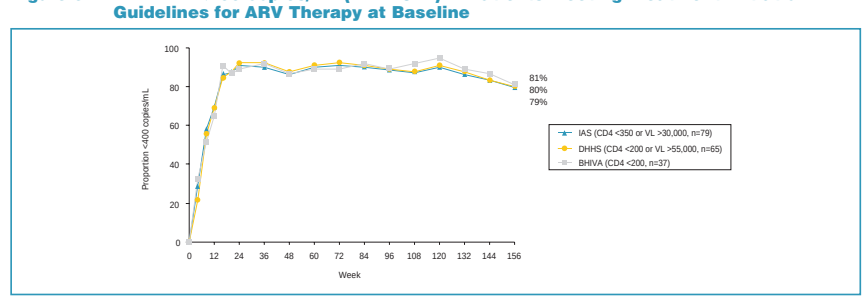
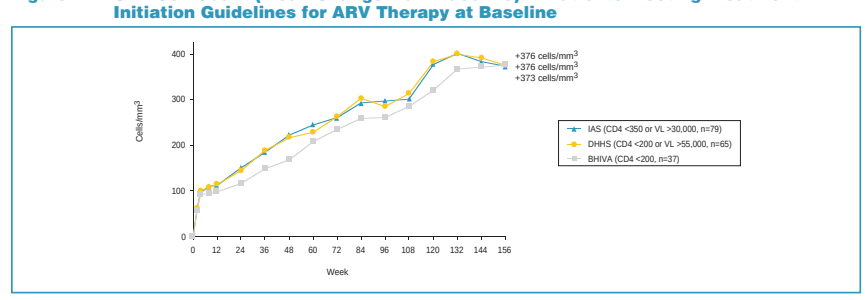


Figure 7. CD4 Cell Count (Mean Change from Baseline) — Patients Meeting Treatment Initiation Guidelines for ARV Therapy at Baseline



CONCLUSIONS

- LPV/r-based therapy exhibits sustained virologic response over long-term follow-up in antiretroviral-naive patients, with 75% (on treatment: 99%) and 76% (on treatment: 96%) of patients demonstrating HIV RNA <400 copies/mL through 156 weeks or <50 copies/mL through 144 weeks, respectively, by ITT NC=F analysis.
- The Kaplan-Meier estimate of the proportion of patients maintaining virologic response through Week 156 was 84.1%.
- Among subjects for whom ARV therapy would be recommended by current treatment guidelines, virologic and immunologic response appear comparable to overall results from the study.
- LPV/r was well tolerated, as indicated by the low rate of study discontinuations due to LPV/r-related adverse events (5/100, 5%).

ACKNOWLEDGMENTS

M97-720 Study Subjects
Covance Central Laboratory Services
AIDS Research Consortium of Atlanta — *Sullivan M*
Beth Israel Deaconess Medical Center — *Fitch H*
Cornell Clinical Trials Unit — *Stroberg T*
Duke University Medical Center — *Giner J, Harmon L*
Northwestern University — *Bruce J*
Pacific Oaks Research — *Perry B, Walker S*
Rush Presbyterian St. Luke's Medical Center — *Narkiewicz E*
Thomas Street Clinic — *Sepcie B*
University of Colorado — *Canmann S, Putnam B, Ray MG*
University of North Carolina at Chapel Hill — *Ngo L*
PPD Development — *McCarley S, Nicks B, Wheat R*
Abbott Laboratories — *Kempf D, Potthoff A, Real K, Rode R, Sheehan K, Yang G*

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