

In a multiple stepwise logistic regression analysis, CD₄ cell count (most recent), prior number of PIs and prior number of NRTIs were found to be independent predictors of viral load response ≤ 500 copies/mL or $\geq 1.0 \log_{10}$ reduction. The results of this analysis are presented in Table 5.

Table 5. Multiple Stepwise Logistic Regression Analysis of Plasma Viral Load (Subjects with Viral Load ≤ 500 copies/mL or $\geq 1.0 \log_{10}$ Decrease from Baseline)

	≤ 500 copies/mL			≤ 500 copies/mL or $\geq 1.0 \log_{10}$ Reduction		
	Odds Ratio	Confidence Intervals	P-Value	Odds Ratio	Confidence Intervals	P-Value
HIV RNA (<100,000, $\geq 100,000$ copies/mL)	0.397	0.292, 0.538	<0.001			
CD ₄ (<50, 50-200, >200)	1.368	1.121, 1.670	0.002	1.353	1.100, 1.665	0.004
PIs (0-2, 3, 4)	0.679	0.574, 0.802	<0.001	0.595	0.485, 0.729	<0.001
NRTIs (0-2, 3-4, 5+)				0.710	0.560, 0.902	0.005
NNRTIs (0, 1, 2+)	0.691	0.564, 0.846	<0.001			

Only SAEs were to be collected per protocol. A summary of SAEs that were reported by two or more LPV/r dosed subjects and of possible, probable or unknown relationship to LPV/r are summarized in Table 6.

Table 6. Serious Adverse Events Reported by Two or More LPV/r Dosed Subjects and of Possible, Probable, or Unknown Relationship to LPV/r*

Body System Adverse Event (COSTART)	Subjects Dosed (N=1772)
Body as a Whole	
Allergic Reaction	2 (0.1%)
Digestive System	
Hepatitis	7 (0.4%)
Pancreatitis	3 (0.2%)
Hepatic Failure	2 (0.1%)
Endocrine System	
Cushings Syndrome	4 (0.2%)
Metabolic and Nutritional Disorders	
Hyperlipemia	2 (0.1%)

* Note: If an event was not assigned a causality either by Abbott or the investigator, it is considered "unknown."

CONCLUSIONS

Spanish subjects are a representative population of this worldwide early access program, with 2077 subjects enrolled. This represents the largest EAP-clinical trial managed to date in Spain.

Subjects enrolled in this EAP represented a heavily pretreated population with the mean number of prior PIs, NRTIs, and NNRTIs of 2.8, 4.3 and 1.1, respectively. In addition, 44.3% of subjects had CDC Class C events prior to enrollment, with the most common inactive AIDS-defining illnesses reported to be esophageal candidiasis (12.1%) and *M. tuberculosis* [pulmonary (6.0%), extrapulmonary (5.7%)].

The majority of the subjects had a virologic response, with significantly higher response rates in subjects who initiated therapy with high baseline CD₄ cell count and less antiretroviral experience.

Kaletra appeared to be well-tolerated with only 3.1% of subjects discontinuing due to adverse events/HIV-related events. Further, no specific SAE was reported for greater than 1% of subjects.

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Efficacy and Safety Results of Lopinavir/r-Based HAART Treatment in Expanded Access Program in Spain Through W24

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INTRODUCTION

Study M99-046 was an open-label, worldwide, early access program (EAP) designed to provide therapy with lopinavir/ritonavir (LPV/r) to subjects who required it prior to its availability through other means. This EAP was initiated in Spain in February 2000 with 51 sites actively participating through August 2001. Due to local regulations, the LPV/r EAP was conducted and managed in Spain as a clinical trial following ICH guidelines for GCP.

OBJECTIVES AND METHODS

Objectives: The objectives of this study were to make LPV/r accessible to HIV-infected subjects who had failed and/or were intolerant to combination therapy with available antiretroviral agents and who had limited remaining treatment options available to them and to obtain additional safety information on LPV/r.

Main Inclusion Criteria: The main inclusion criteria prior to dosing were: ≥ 12 years of age, confirmed laboratory diagnosis of HIV infection, medically stable in the opinion of the investigator, unable to construct a viable treatment regimen without LPV/r, and no liver dysfunction as evidenced by a liver function test result less than 5 times the upper limit of normal. Initial study entry criteria included CD₄ counts < 50 cells/mm³ or a history of an AIDS-defining opportunistic infection while on highly active antiretroviral therapy (HAART), HIV RNA level $\geq 10,000$ copies/mL, and failure on at least 2 prior protease inhibitors; however, these specific criteria were removed after approximately 5 months of enrollment in the global EAP and were no longer applicable by the time most Spanish sites started to enroll subjects in the study.

Study Procedures: Study visits were to be scheduled monthly for the first 6 months and every other month thereafter. Throughout the study, CD₄, HIV-RNA, SAE and reasons for discontinuations were recorded. Virologic (plasma HIV RNA) and immunologic (CD₄ cell counts) measurements, were reported at the discretion of the investigators, and were obtained as part of the standard of care of the subjects.

Study Drug Treatment: All subjects entering this EAP were to be given LPV/r (400 mg/100 mg BID)* in combination with other antiretroviral agents, which were selected by the investigator, in order to construct a viable treatment regimen for each subject.

*Note: The protocol allowed the dose of LPV/r to be increased to 533 mg/133 mg BID when given concomitantly with either efavirenz or nevirapine.

RESULTS

From March 2000 to June 2001, a total of 2077 subjects were enrolled in this study in Spain (Figure 1). Of these subjects, 1772 have documentation available indicating that they had initiated dosing with LPV/r on or before August 7, 2001.

Figure 1a. Cumulative Number of Subjects and Active Sites in Spain in LPV/r EAP

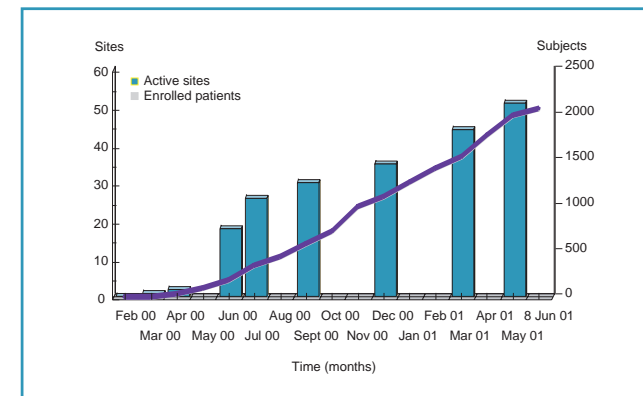
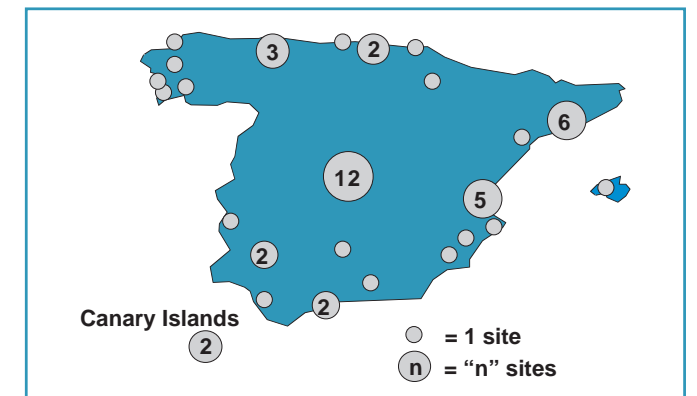


Figure 1b. EAP-LPV/r: Active Sites Distribution in Spain



Summary of Demographic and Baseline Disease Characteristics

Demographic and disease characteristics for all subjects who initiated dosing with LPV/r are summarized in Table 1. The mean baseline HIV RNA and CD₄ count for these subjects were 4.37 log₁₀/mL and 277.1 cells/mm³, respectively. In addition, 44.3% of these subjects had experienced at least 1 CDC Class C (AIDS-defining) event.

Table 1. Summary of Demographic and Baseline Disease Characteristics

Demographic or Disease Characteristic	LPV/r Dosed Subjects (N=1772)	Demographic or Disease Characteristic	LPV/r Dosed Subjects (N=1772)
Gender		Karnofsky Score	
Male	74.2%	Mean (SD)	96.2 (7.9)
Female	23.3%	CD₄ Count (cells/mm³) – Most Recent	
Not specified	2.5%	<50	12.1%
Race		50-100	9.7%
Caucasian	96.2%	101-200	21.1%
Black	0.3%	201-400	29.1%
Asian/Pacific Islander	0.3%	>400	21.2%
Other	0.4%	Not Specified	6.9%
Not Specified	2.8%	Mean (SD)	277.1 (240.5)
Age (years)		HIV RNA (log₁₀ copies/mL)	
Mean (SD)	39.2 (7.7)	<3.0	12.8%
History of Hepatic Insufficiency		3.0-3.9	17.7%
Yes	2.9%	4.0-4.9	35.0%
History of Renal Insufficiency		5.0-5.9	24.8%
Yes	0.7%	6.0-6.9	2.3%
CDC Classification		Not Specified	7.6%
A: Asymptomatic, Acute (primary) HIV or persistent generalized lymphadenopathy	22.6%	Mean (SD)	4.37 (0.97)
B: Symptomatic, Not A or C conditions	23.6%	Prior ARV Use (Mean)	
C: AIDS – Indicator Conditions	44.3%	NRTIs	4.3
Not Specified	9.5%	PIs	2.8
		NNRTIs	1.1

Of the 1772 subjects who initiated dosing with LPV/r in this EAP, 1605 have data available on AIDS-defining illnesses at screening (Table 2).

As of August 7, 2001, the mean duration of follow-up for subjects with confirmed LPV/r dosing was 7.72 months. Sixty-one percent (61.0%) of the subjects participated in this EAP for at least 6 months. A summary of baseline antiretroviral medications used in combination with LPV/r are presented in Table 3.

Table 2. Summary of Most Commonly Reported “Active/Inactive” AIDS-Defining Illnesses at Screening

Disease	Subjects (N=1605)
Active (≥0.5% of subjects)	
Esophageal candidiasis	0.9%
HIV related wasting syndrome	0.9%
Kaposi's sarcoma	0.6%
Inactive (≥2% of subjects)	
Esophageal candidiasis	12.1%
Pulmonary <i>M. tuberculosis</i>	6.0%
Extrapulmonary <i>M. tuberculosis</i>	5.7%
<i>Pneumocystis carinii</i> pneumonia	4.4%
Kaposi's sarcoma	2.8%
CMV retinitis	2.1%

Table 3. Summary of Antiretroviral Medication Use^a

Antiretroviral Medication	Baseline ARV Use (N=1742)
Protease Inhibitors	
Indinavir	3.3%
Nelfinavir	0.3%
Saquinavir ^b	9.1%
Amprenavir	0.7%
Nucleoside Reverse Transcriptase Inhibitors	
Stavudine (d4T)	55.2%
Zidovudine ^c (AZT, ZDV)	13.1%
Abacavir	51.4%
Didanosine (ddI)	51.2%
Zalcitabine (ddC)	0.5%
Lamivudine^b (3TC)	33.5%
Non-Nucleoside Reverse Transcriptase Inhibitors	
Nevirapine	5.8%
Efavirenz	21.2%
Other Agents	
Hydroxyurea	2.2%
Tenofovir (PMPA)	0.9%
T-20	0.2%

^a Those treatments used in more than 20% of subjects are highlighted.
^b Includes use of Fortovase or Invirase.
^c Includes use of Zidovudine or Combivir, and Lamivudine or Combivir, respectively.

The mean baseline status of the subject population shifted to less antiretroviral-experienced, healthier subjects over time. Figure 2 displays the mean CD₄ cell count (most recent) at screening, while Figure 3 displays the mean number of prior NRTIs, PIs, and NNRTIs used prior to initiation of LPV/r therapy, for subjects enrolled in Spain.

Figure 2. Mean CD₄ Count for Subjects Initiating LPV/r Therapy

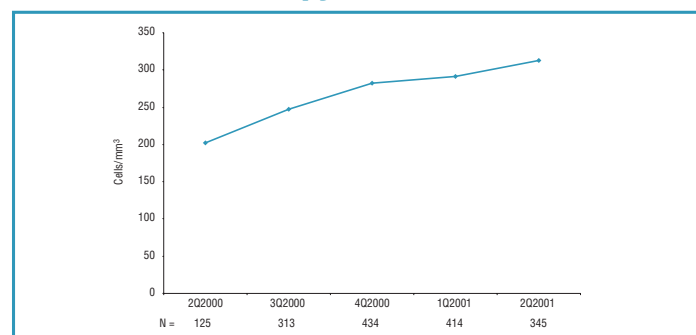
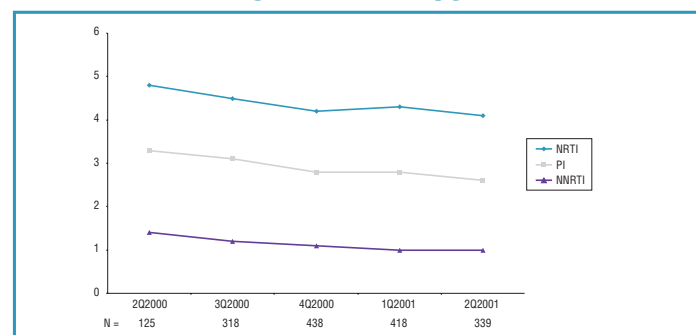


Figure 3. Mean Number of ARVs Used Prior to Initiating LPV/r Therapy



Efficacy and Safety

As of August 7, 2001, a total of 356 (20.1%) of the 1772 subjects dosed with LPV/r have been discontinued from the study. The disposition of those subjects who initiated dosing with LPV/r is summarized in Table 4. The majority of the subjects that discontinued have done so due to the availability of Kaletra by other means.

Table 4. Summary of Documented Subject Disposition

Subjects Dosed with LPV/r	1772
Subjects Prematurely Discontinued ^a	20.1%
Withdrew Consent	0.9%
Adverse Event/HIV-related Event	3.1%
Subject Death	1.5%
Lost to Follow-up	1.0%
Administrative (commercial availability)	10.9%
Other	3.0%

^a More than 1 reason for discontinuation may have been selected.

Virologic response (defined as either a plasma HIV RNA measurement at or below 500 copies/mL* or at least a 1.0 log₁₀ copies/mL decrease from baseline) was further evaluated as a function of baseline HIV RNA (<100,000, ≥100,000 copies/mL), baseline CD₄ count (<50 cells/mm³, 50-200 cells/mm³, >200 cells/mm³), prior protease inhibitor use (0-2, 3, 4), prior NRTI use (0-2, 3-4, 5+) and prior NNRTI use (0, 1, 2+). Also, the use of NNRTI as a new class was evaluated. Results are summarized in Figures 4-9.

*Note: Since a central laboratory was not used for determination of plasma viral load, and several different viral load assays could have been used, a “standardized” cutoff of 500 copies/mL was used in the assessment of plasma viral load measurements.

Figure 4. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log₁₀ Below Baseline Stratified by Baseline HIV RNA

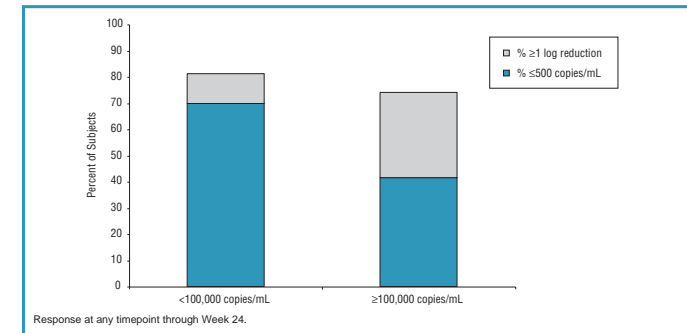


Figure 5. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log₁₀ Below Baseline Stratified by Baseline CD₄ Cell Count

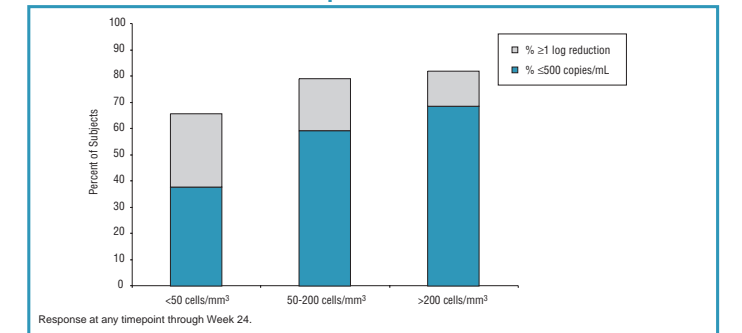


Figure 6. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log₁₀ Below Baseline Stratified by Prior PI Use

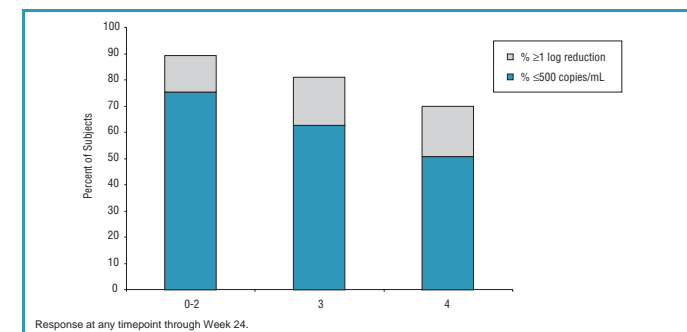


Figure 7. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log₁₀ Below Baseline Stratified by Prior NRTI Use

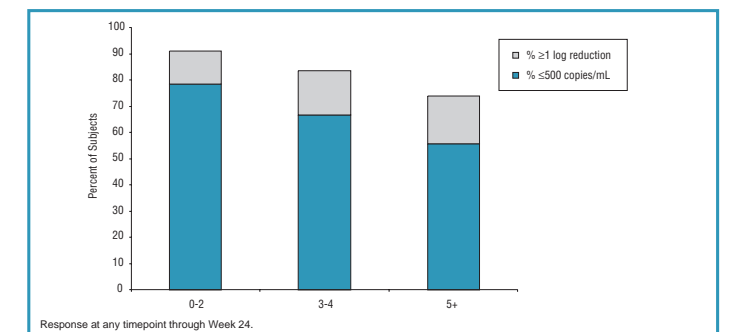


Figure 8. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log₁₀ Below Baseline Stratified by Prior NNRTI Use

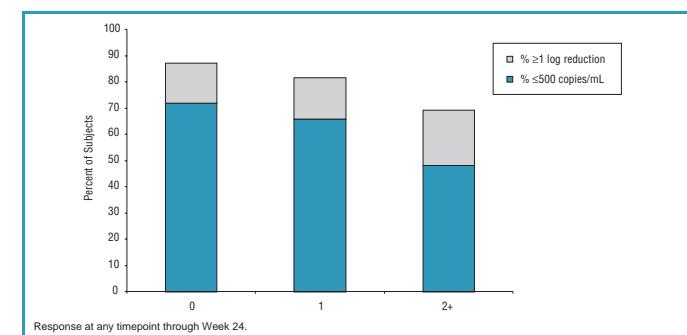


Figure 9. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log₁₀ Below Baseline Stratified by the Use of NNRTI as a New Class

