Poster #233

8th European Conference on Clinical Aspects and Treatment of HIV-Infection, Athens, Greece, October 2001

Initial Efficacy and Safety Results from the Lopinavir/ritonavir (LPV/r, Kaletra™) Early Access Program in Italy

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BACKGROUND

Study M99-046 was an open-label, worldwide, early access program (EAP) designed to provide therapy with Kaletra™ (lopinavir/ritonavir, LPV/r) to subjects who had failed and/or were intolerant to combinations of available antiretroviral agents and who had limited remaining treatment options available to them. This EAP was initiated globally in September 1999 and afforded subjects who had a serious and life-threatening disease the earliest possible access to a promising therapy.

OBJECTIVES AND DESIGN

To be eligible for participation in the study, subjects must have met the following criteria prior to dosing: ≥12 years of age, confirmed laboratory diagnosis of HIV infection, medically stable in the opinion of the investigator, did not require and agreed not to take prohibited medication, unable to construct a viable treatment regimen without LPV/r, had no liver dysfunction as evidenced by a liver function test result less than 5 times the upper limit of normal, was not participating in an existing LPV/r clinical trial, or, if female, was not pregnant or breast-feeding and agreed to use an effective barrier contraceptive method while receiving LPV/r. Initial study entry criteria included CD_4 counts <50 cells/mm^3 or a history of an AIDS-defining opportunistic infection while on highly active antiretroviral therapy (HAART), HIV RNA level ≥10,000 copies/mL, and failure on at least 2 prior protease inhibitors; however, these CD_4 and HIV RNA criteria were removed prior to the start of this EAP in Italy.

All subjects entering this EAP were to be given LPV/r in combination with other antiretroviral agents. The dose of LPV/r was 400 mg/100 mg BID; however, 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. Other antiretroviral agents to be given in combination with LPV/r were selected by the investigator, in order to construct a viable treatment regimen for each subject.

RESULTS FOR ITALY

A total of 1411 subjects were enrolled in Italy. Of these subjects, 1265 have documentation available indicating that they had initiated dosing with LPV/r. A summary of the available data from the EAP in Italy through August 7, 2001 is presented below.

Subject Disposition

Of the 1265 subjects who initiated LPV/r therapy in this EAP, 462 (36.5%) have been discontinued from the study. The percentage of subjects who discontinued due to an adverse event/HIV-related event, death, lost to follow-up or withdrawal of consent was 6.3%, 1.4%, 2.5%, and 1.7%, respectively. The disposition of those subjects dosed with LPV/r is summarized in Table 1.

Table 1. Summary of Documented Subject Disposition

Subjects Dosed	1265
Subjects Discontinued (%)[a]	36.5
Withdrew Consent	1.7
Adverse Event/HIV-related Event	6.3
Subject Death	1.4
Loss to Follow-up	2.5
Administrative	21.1
Other	4.2

[a] More than one reason for discontinuation may have been selected.

Following the approval and commercial availability of Kaletra in Italy, study closeout procedures for this EAP were implemented, and investigators began supplying subjects with Kaletra through other means. This accounts for the large percentage of subjects (21.1%) who have discontinued due to administrative reasons.

Demographic and Other Characteristics of the Study Population

The majority of the 1265 subjects who initiated dosing with LPV/r were male (67.6%; 855/1265) and most were Caucasian (88.0%;1113/1265). Demographic characteristics for all subjects who initiated dosing with LPV/r are summarized in Table 2.

Table 2. Summary of Demographic Characteristics

Variable	LPV/r (n=1265)
Gender (%)	
Male	67.6
Female	23.6
Not specified	8.9
Race (%)	
Caucasian	88.0
Black	1.1
Asian/Pacific Islander	0.3
Other	1.3
Not Specified	9.3
Age (years)	
Mean (SD)	39.9 (7.6)

Approximately 39% of the subjects dosed with LPV/r in this EAP were categorized as Centers for Disease Control (CDC) Class C, indicating that these subjects had experienced an AIDS-indicator condition at some time during the course of their HIV infection. More than 70% of the subjects had HIV RNA levels ≥4.0 $\log_{10}$ copies/mL prior to entering the study. The mean baseline HIV RNA and CD_4 counts were 4.66 $\log_{10}$ copies/mL and 224.4 cells/mm^3, respectively. A summary of the disease characteristics obtained at screening for all subjects who initiated dosing with LPV/r is presented in Table 3.

Table 3. Summary of Screening Characteristics

Characteristic	LPV/r (N=1265)	
History of Hepatic Insufficiency (%)		
Yes	32.8	
History of Renal Insufficiency (%)		
Yes	1.3	
CDC Classification (%)		
A: Asymptomatic, Acute (primary) HIV or persistent generalized lymphadenopathy	22.0	
B: Symptomatic, Not A or C conditions	24.7	
C: AIDS – Indicator Conditions	39.1	
Not Specified	14.2	
Karnofsky Score		
Mean (SD)	91.6 (11.1)	
CD_4 count (cells/mm^3)	**Most Recent**	**Nadir**
<50	14.9%	33.4%
50 – 100	13.1%	18.7%
101 – 200	19.7%	20.2%
201 – 400	26.9%	13.0%
<400	13.8%	1.7%
Not Specified	11.6%	13.0%
Mean (SD)	224.4 (201.3)	107.1 (111.4)
HIV RNA ($\log_{10}$ copies/mL) – Most Recent		
<3.0	5.4%	
3.0 - <4.0	11.3%	
4.0 - <5.0	37.7%	
5.0 - <6.0	30.7%	
6.0 - <7.0	2.4%	
Not Specified	12.6%	
Mean (SD)	4.66 (0.83)	

Of the 1265 subjects who initiated dosing, 1087 have data available on AIDS-defining illnesses at screening. The most commonly reported "active" AIDS-defining illness at screening in these subjects was HIV-related wasting syndrome (1.2%; 13/1087). The most commonly reported "inactive" AIDS-defining illnesses at screening were esophageal candidiasis (10.9%; 119/1087), *Pneumocystis carinii* pneumonia (5.5%; 60/1087), pulmonary *Mycobacterium tuberculosis* (3.1%; 34/1087), toxoplasmosis of the brain (2.8%; 30/1087), CMV retinitis (2.7%; 29/1087), Kaposi's sarcoma (2.4%; 26/1087), and extrapulmonary cryptococcosis (2.3%; 25/1087).

Extent of Exposure

The first subject initiated LPV/r therapy in Italy on June 15, 2000. The mean duration of follow-up through August 7, 2001 for subjects with confirmed dosing was 6.83 months, with approximately 60% of the subjects participating in this EAP for a minimum of 6 months.

Antiretroviral Medications

Of the 1265 subjects who initiated LPV/r, a brief history of antiretroviral medications used prior to initiation of LPV/r is available for 1100 subjects. The mean number of protease inhibitors, NRTIs and NNRTIs used by these subjects prior to initiation of LPV/r was 2.9, 4.3 and 1.0, respectively. A summary of antiretroviral medications used prior to enrollment and baseline antiretroviral medications used in combination with LPV/r are presented in Table 4.

Table 4. Summary of Antiretroviral Medication Use

Antiretroviral Medication	Prior ARV Use (N=1100)	Baseline ARV Use (N=1246)
Protease Inhibitors (%)		
Indinavir	82.6	2.1
Nelfinavir	65.7	0.6
Ritonavir	66.7	0.0
Saquinavir[a]	69.5	1.6
Amprenavir	10.2	4.3
Nucleoside Reverse Transcriptase Inhibitors (%)		
Stavudine (d4T)	92.6	51.9
Zidovudine[b] (AZT, ZDV)	92.6	22.6
Abacavir	32.8	31.1
Didanosine (ddI)	80.3	39.2
Zalcitabine (ddC)	41.5	3.2
Lamivudine[b] (3TC)	93.6	42.5
Non-Nucleoside Reverse Transcriptase Inhibitors (%)		
Delavirdine	4.8	0.0
Nevirapine	51.5	4.7
Efavirenz	42.5	15.1
Nucleotide Analogues (%)		
Adefovir dipivoxil	0.5	0.0
Tenofovir (PMPA)	0.3	0.0
Other Agents (%)		
Hydroxyurea	6.5	0.4
T-20	0.3	0.1

Note: Of the 246 subjects reported to be taking ritonavir immediately prior to initiation of LPV/r, 100% (246/246) discontinued the use of ritonavir when switching to LPV/r.

[a] Includes use of Fortovase or Invirase.

[b] Includes use of Zidovudine or Combivir, and Lamivudine or Combivir, respectively.

Baseline Characteristics of the Study Population over Time

The mean baseline status of the subject population shifted to less antiretroviral-experienced, healthier subjects over time. Figure 1 displays the mean CD_4 cell count (most recent) at screening, while Figure 2 displays the mean number of NRTIs, PIs, and NNRTIs used prior to initiation of LPV/r therapy for subjects enrolled in Italy.

Figure 1. Mean CD_4 Cell Count for Subjects Initiating LPV/r Therapy

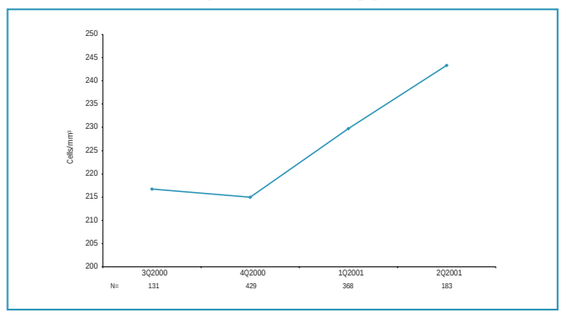
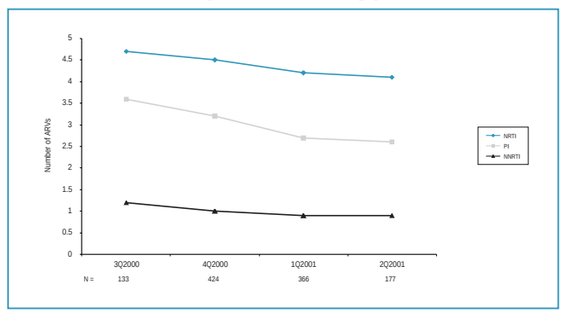


Figure 2. Mean Number of ARVs Used Prior to Initiating LPV/r Therapy



Virologic and Immunologic Response

Virologic (plasma HIV RNA) and immunologic (CD_4 cell counts) measurements, which were reported at the discretion of the investigators, were to be obtained as part of the standard of care of the subjects. In addition, investigators utilized local laboratories for the determination of virologic and immunologic measurements. 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.

Plasma viral load measurements were evaluated as a function of baseline HIV RNA (<100,000, ≥100,000 copies/mL), baseline CD_4 count (<50 cells/mm^3, 50-200 cells/mm^3, >200 cells/mm^3), prior protease inhibitor use (0-2, 3, 4), prior NRTI use (0-2, 3-4, 5+) and prior NNRTI use (0, 1, 2+). The use of NNRTI as a new class was also evaluated. Viral load response has been defined as either a plasma HIV RNA measurement at or below 500 copies/mL or at least a 1.0 $\log_{10}$ copies/mL decrease from baseline (for those subjects who did not achieve a measurement at or below 500 copies/mL). Results through 24 weeks are summarized in Figures 3-5.

Figure 3. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 $\log_{10}$ copies/mL Below Baseline Stratified by Baseline Viral Load and CD_4 Cell Count

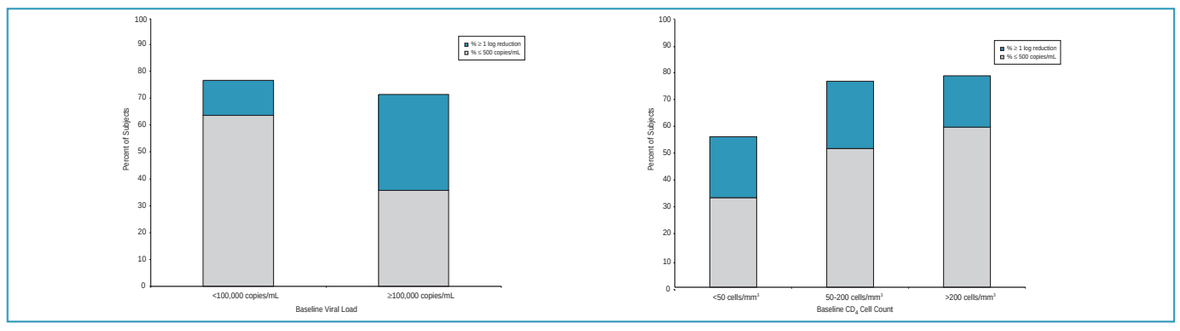


Figure 4. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 $\log_{10}$ copies/mL Below Baseline Stratified by Prior PI Use and Prior NRTI Use

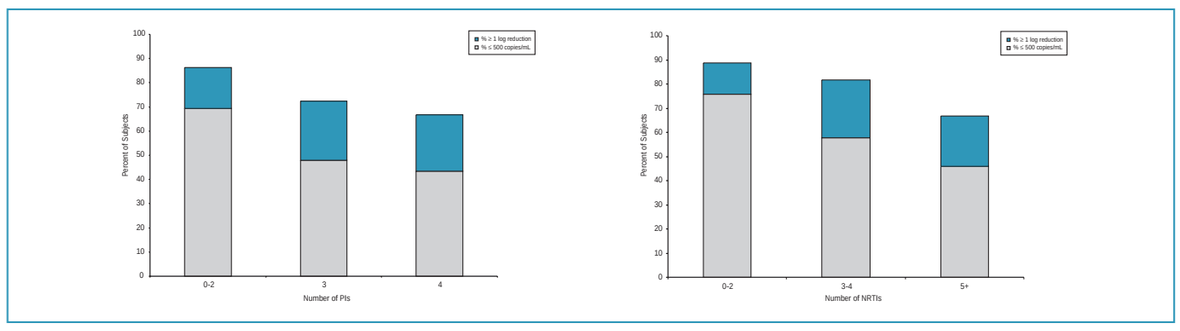
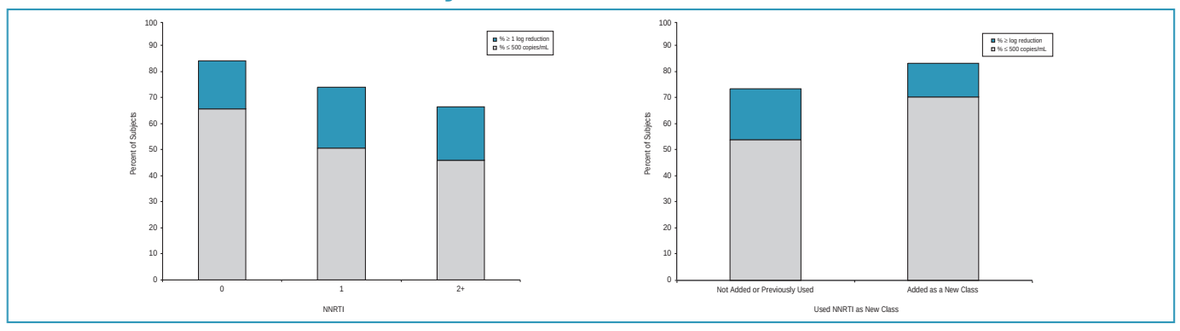


Figure 5. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 $\log_{10}$ copies/mL Below Baseline Stratified by Prior NNRTI Use and the Use of an NNRTI as a New Class



In a multiple stepwise logistic regression analysis, plasma HIV RNA, CD_4 cell count, prior number of PIs, prior number of NRTIs and the addition of an NNRTI as a new class were found to be independent predictors of viral load response ≤500 copies/mL ($p<0.10$). In a separate multiple "stepwise" logistic regression analysis, CD_4 cell count, prior number of PIs, prior number of NRTIs, and the addition of an NNRTI as a new class were found to be independent predictors of viral load response ≤500 copies/mL or ≥1.0 $\log_{10}$ reduction ($p<0.10$).

Table 6. Multiple Stepwise Logistic Regression Analysis of Plasma Viral Load (Subjects with Viral Load ≤500 copies/mL or ≥1.0 $\log_{10}$ Decrease from Baseline)

	<500 copies/mL		≤500 copies/mL or ≥1.0 $\log_{10}$ Reduction	
	Odds Ratio	**Confidence Intervals**	**Odds Ratio**	**Confidence Intervals**
HIV RNA (<100,000, ≥100,000 copies/mL)	0.369	0.268, 0.508		
CD_4 (<50, 50-200, >200)	1.283	1.033, 1.593	1.562	1.250, 1.952
PIs (0-2, 3, 4)	0.699	0.578, 0.846	0.721	0.580, 0.896
NRTIs (0-2, 3-4, 5+)	0.719	0.556, 0.930	0.561	0.414, 0.762
Add NNRTI as new class	1.755	0.962, 3.202	2.053	0.901, 4.675

Note: Prior NNRTI use was not found to be a significant predictor of virologic response in either multiple stepwise logistic regression analysis ($p>0.10$). (Reference: R. Reitmayer, R. Rode, B. Bernstein, et al. Results from the Kaletra™ Early Access program. Poster 8th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, Feb 4-8, 2001.)

Adverse Events

Per protocol, only serious adverse event (SAE) data were collected. Overall, no specific adverse event of possible, probable or unknown relationship to LPV/r was reported by ≥1% of the subjects who received LPV/r. A summary of SAEs that were of possible, probable or unknown relationship to LPV/r and occurred in ≥2 subjects are summarized in Table 7.

Table 7. Serious Adverse Events of Possible, Probable, or Unknown Relationship to LPV/r in Subjects Who Initiated Therapy with LPV/r

Body System Adverse Event (COSTART)	LPV/r (N=1265)
Body as a Whole	
Fever	3 (0.2%)
Allergic Reaction	2 (0.2%)
Digestive System	
Vomiting	3 (0.2%)
Liver Function Tests Abnormal	3 (0.2%)
Nausea	2 (0.2%)
Hepatitis	2 (0.2%)
Metabolic and Lymphatic System	
Hyperlipemia	3 (0.2%)
Lactic Acidosis	2 (0.2%)
Skin and Appendages	
Rash	3 (0.2%)

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

CONCLUSION

- The majority of subjects treated with LPV/r experienced a virologic response, with significantly higher virologic response rates in subjects with low baseline viral load, high baseline CD_4, less antiretroviral medication use (especially PI and NRTI use), and the addition of an NNRTI as a new class of antiretroviral therapy.
- The safety and tolerability profile of LPV/r, observed in previous randomized clinical trials in ARV-naïve and ARV-experienced populations, is confirmed in this EAP: LPV/r was generally well-tolerated in the Italian EAP (which mostly enrolled highly ARV-experienced subjects), and no specific serious adverse event was reported in greater than 1% of the subject population.

ACKNOWLEDGMENTS

Abbott Italy would like to acknowledge the large number of patients and physicians who have taken part in the Kaletra™ EAP, and the groups that provided assistance with its development and implementation (representatives of the advocacy groups: ICAB and GITA).