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Efficacy and Safety Results from the LPV/r Early Access Program in Germany

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INTRODUCTION

Study M99-046 was one of several programs designed to make Kaletra™ (lopinavir/ritonavir, 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. Another objective was to obtain additional safety information on LPV/r. Germany was one of 35 countries to participate in this Early Access program (EAP). Worldwide more than 11,000 subjects have been provided with Kaletra, as co-formulated lopinavir/ritonavir capsules, through this EAP.

The LPV/r dose was 400 mg/100 mg BID; however, if efavirenz or nevirapine was administered concomitantly, the protocol allowed the dose of LPV/r to be increased to 533 mg/133 mg BID. 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.

A total of 729 subjects were enrolled in the EAP in Germany.

METHODS

Due to the nature of the EAP, limited safety and efficacy data were collected. Reporting of serious adverse events (SAEs) was required. 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. As 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. Subjects with baseline HIV RNA ≤500 copies/mL were excluded from analysis of the efficacy data. 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, SGOT/SGPT (AST/ALT) <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 specific criteria were removed approximately 2 months after enrollment was initiated in Germany.

RESULTS

The first subject initiated LPV/r therapy in Germany on December 22, 1999. As of August 7, 2001, the mean duration of follow-up for subjects with confirmed LPV/r dosing was 4.46 months. Of the 729 subjects enrolled in Germany, 684 have documentation available indicating that they had initiated dosing with LPV/r.

Summary of Demographic and Disease Characteristics

The mean baseline HIV RNA and CD_4 count were 4.41 log_{10} copies/mL and 215.3 cells/mm^3, respectively. Approximately 57% of the subjects dosed with LPV/r 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. Demographic and disease characteristics are presented in Table 1.

Table 1. Summary of Baseline Demographic and Disease Characteristics

Demographic or Disease Characteristic	LPV/r (N=684)	
Gender (%)		
Male	87.1	
Female	11.7	
Not specified	1.2	
Race (%)		
Caucasian	91.4	
Black	4.7	
Asian/Pacific Islander	0.7	
Other	1.6	
Not Specified	1.6	
Age (years)		
Mean (SD)	43.0 (9.2)	
CDC Classification (%)		
A: Asymptomatic, Acute (primary) HIV or persistent generalized lymphadenopathy	7.9	
B: Symptomatic, Not A or C Conditions	31.7	
C: AIDS – Indicator Conditions	57.2	
Not Specified	3.2	
Karnofsky Score		
Mean (SD)	88.3 (11.5)	
CD_4 count (cells/mm^3)	Most Recent	Nadir
<50	20.2 %	40.5 %
50 – 100	13.9 %	18.7 %
101 – 200	21.5 %	20.5 %
201 – 400	26.3 %	12.3 %
>400	15.1 %	2.0 %
Not Specified	3.1 %	6.0 %
Mean (SD)	215.3 (191.9)	104.9 (118.2)
HIV RNA (log_{10} copies/mL) – Most Recent		
<3.0	15.8 %	
3.0 - <4.0	13.5 %	
4.0 - <5.0	34.8 %	
5.0 - <6.0	31.1 %	
6.0 - <7.0	1.6 %	
Not Specified	3.2 %	
Mean (SD)	4.41 (1.00)	

Antiretroviral Medications

Of the 684 subjects who initiated LPV/r, a brief history of antiretroviral medications used prior to the initiation of LPV/r is available for 647 subjects. The mean number of protease inhibitors, NRTIs and NNRTIs used by these subjects prior to the initiation of LPV/r was 3.0, 4.6, and 1.2, respectively. A summary of antiretroviral medications used prior to enrollment in this EAP and baseline antiretroviral medications used in combination with LPV/r are presented in Table 2.

Table 2. Summary of Antiretroviral Medication Use

Antiretroviral Medication	Prior ARV Use (N=647)	Baseline ARV Use (N=674)
Protease Inhibitors (%)		
Indinavir	75.4	1.6
Nelfinavir	57.2	0.9
Ritonavir	75.7	0.0
Saquinavir[a]	66.9	2.7
Amprenavir	26.7	7.4
Nucleoside Reverse Transcriptase Inhibitors (%)		
Stavudine (d4T)	88.4	45.5
Zidovudine[b] (AZT, ZDV)	92.6	30.6
Abacavir	63.8	39.2
Didanosine (ddI)	77.4	45.3
Zalcitabine (ddC)	43.7	3.0
Lamivudine[b] (3TC)	96.0	51.9
Non-Nucleoside Reverse Transcriptase Inhibitors (%)		
Delavirdine	8.8	0.1
Nevirapine	51.5	14.4
Efavirenz	58.7	15.7
Loviride	0.6	0.0
Nucleotide Analogues (%)		
Adefovir dipivoxil	0.8	0.1
Other Agents (%)		
Hydroxyurea	14.7	1.9
L-667	0.2	0.0

Note: Of the 190 subjects reported to be taking ritonavir immediately prior to initiation of LPV/r, 100% (190/190) 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

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

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

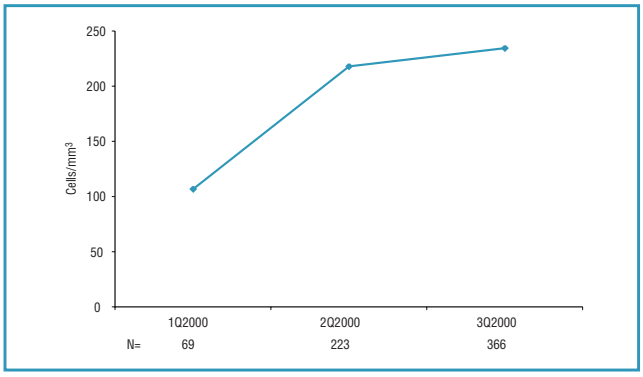
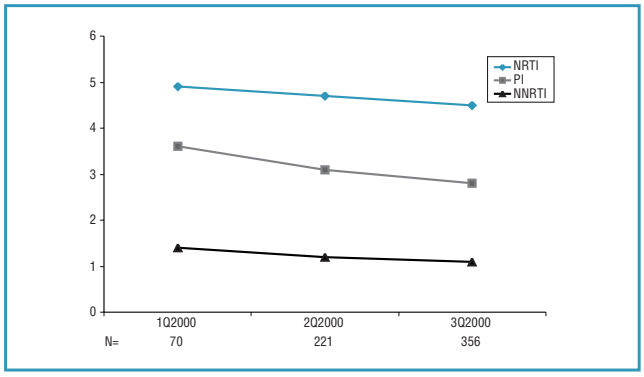


Figure 2. Mean Number of ARVs Used Prior to Initiating LPV/r Therapy



Viral Load Response Stratified by Baseline Characteristics

Plasma viral load measurements were further evaluated as a function of baseline HIV RNA (<100,000, ≥100,000 copies/mL), baseline CD_4 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+) through the first 24 weeks of the program. 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). Overall, 55.6% of the subjects dosed had a viral load response of ≤500 copies mL, and 74.4% of the subjects dosed had a viral load response of ≤500 copies/mL or at least a 1.0 $\log_{10}$ decline from baseline. Results are summarized in Figures 3-8.

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

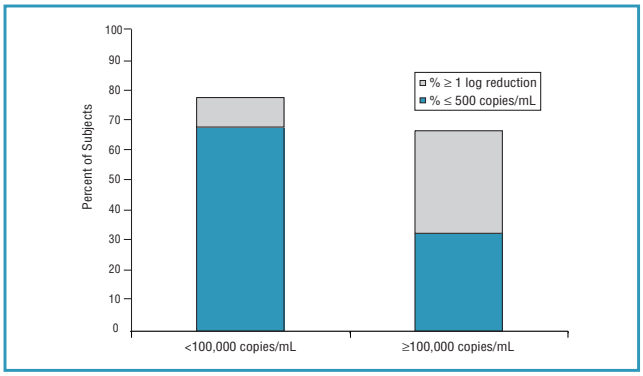


Figure 4. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 $\log_{10}$ Below Baseline Stratified by Baseline CD_4 Cell Count

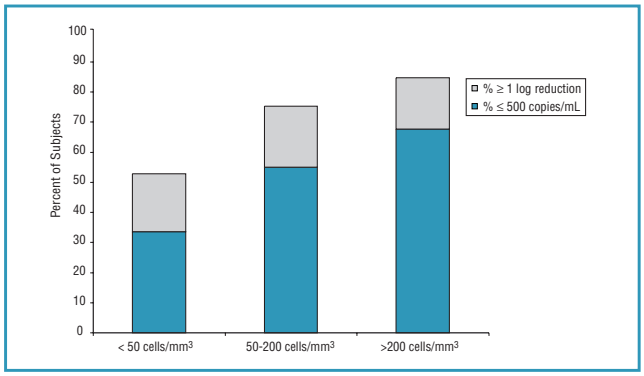


Figure 5. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 $\log_{10}$ Below Baseline Stratified by Prior PI Use

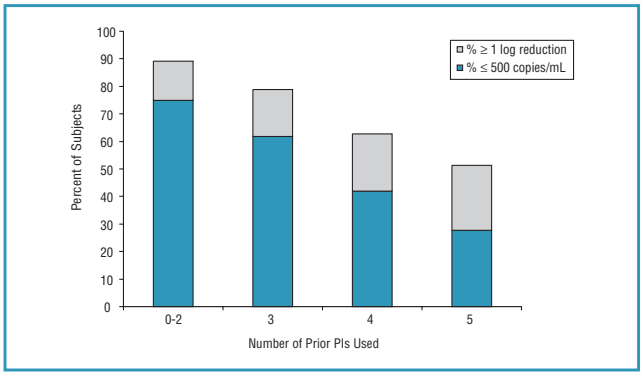


Figure 6. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 $\log_{10}$ Below Baseline Stratified by Prior NRTI Use

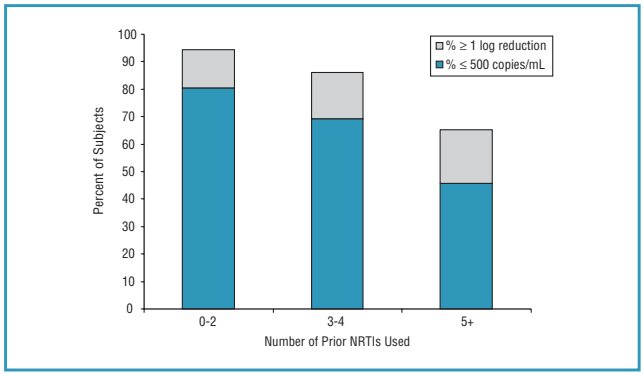


Figure 7. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log_{10} Below Baseline Stratified by Prior NNRTI Use

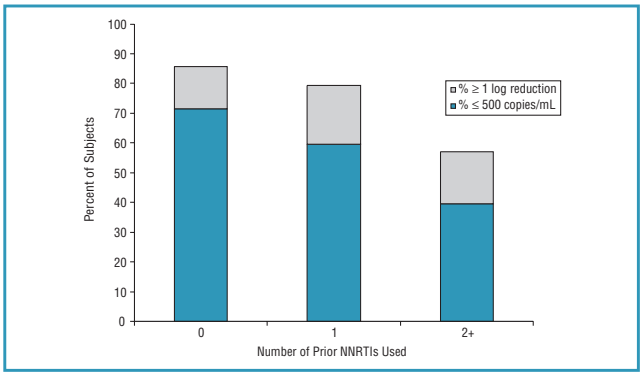
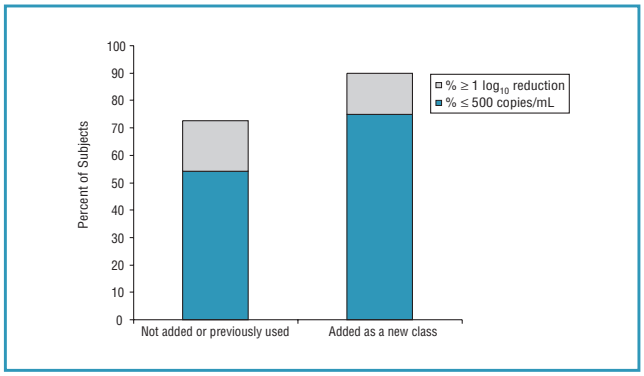


Figure 8. Percent of Subjects with Viral Load Nadir ≤500 copies/mL or ≥1.0 log_{10} Below Baseline Stratified by the Use of NNRTI as a New Class



Based on results from a multivariate stepwise logistic regression analysis, plasma HIV RNA, CD_4 cell count, prior number of PIs used, and prior number of NNRTIs used were found to be independent predictors of viral response, as defined by a plasma viral load ≤500 copies/mL during the first 24 weeks of LPV/r therapy (p<0.10). In addition, CD_4 cell count, prior number of PIs used, prior number of NRTIs used, and prior number of NNRTIs used were found to be independent predictors of viral response, as defined by a plasma viral load ≤500 copies/mL or a viral load reduction of ≥1.0 log_{10} copies/mL during the first 24 weeks of LPV/r therapy (p<0.10). Results from the multivariate stepwise logistic regression analyses are summarized in Table 3.

Table 3. Multivariate 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)	0.261	0.165, 0.412		
CD_4 (<50, 50-200, >200)	1.429	1.070, 1.908	2.050	1.518, 2.770
PIs (0-2, 3, 4)	0.560	0.449, 0.700	0.684	0.530, 0.883
NRTIs (0-2, 3-4, 5+)			0.504	0.299, 0.850
NNRTIs (0, 1, 2+)	0.726	0.515, 1.023	0.652	0.441, 0.965

Although the use of an NNRTI as a new class was not found to be an independent predictor of viral load response in this analysis of data from the EAP in Germany, it was found to be a predictor of viral load response in a previous analysis that included all subjects participating in the EAP. (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.)

Safety Results

A total of 684 subjects initiated LPV/r in Germany. The majority (70.6%) of the subjects were discontinued from this EAP as a result of the commercial availability of LPV/r (Kaletra™). The disposition of these subjects is summarized in Table 4.

Table 4. Summary of Documented Subject Disposition

Subjects Dosed (N)	684
Subjects Discontinued (%)[a]	93.4
Withdrew Consent	2.3
Adverse Event/HIV-related Event	5.8
Subject Death	1.3
Lost to Follow-up	4.2
Administrative	70.6
Other	10.1

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

Per protocol, only serious adverse event (SAE) data were collected in the EAP. 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. The only SAE reported for 2 or more subjects participating in Germany was pancreatitis (3/684 [0.4%]).

CONCLUSIONS

- More than 650 subjects in Germany were provided with Kaletra through the EAP in Germany.
- In spite of extensive prior ARV treatment, with a mean number of 3.0 PIs, 4.6 NRTIs, and 1.2 NNRTIs, 56% of subjects achieved viral loads ≤500 copies/mL. An overall virologic response defined as a plasma HIV RNA result ≤500 copies/mL or ≥1.0 log_{10} copies/mL reduction was achieved by approximately 74% of the subjects.
- No specific serious adverse event was reported in greater than 1% of the subject population.

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