

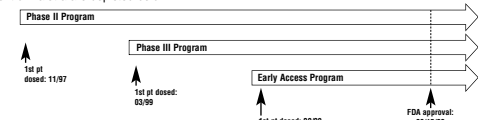


Results from the Kaletra™ Early Access Program

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BACKGROUND

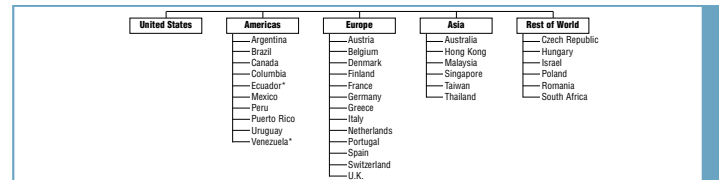
Expanded Access Programs (EAP) are conducted to provide patients with access to potentially life-saving medications prior to marketing authorization for use. Such programs are conducted after sufficient evidence of the safety and effectiveness of the medication has been demonstrated, usually in Phase II clinical trials, and while Phase III clinical trials are ongoing. Kaletra™ is a co-formulation of lopinavir and ritonavir, with ritonavir employed solely as a pharmacokinetic enhancer. Kaletra was first used in an HIV-infected patient in November 1997 and the FDA granted approval for commercial use of Kaletra in the United States (US) on September 15, 2000. Major milestones in the clinical development of Kaletra are depicted below.



KALETRA EAP SCOPE AND LOGISTICS

Scope of Program
The goal of this global EAP was to provide Kaletra to HIV-infected patients with no other treatment options available, as early in clinical development and under as simple an enrollment process as possible. The Kaletra EAP was initiated while the Phase III clinical trial program was enrolling, approximately one year prior to the first approval of Kaletra for commercial use. Over 35 countries will participate in the Kaletra EAP before its completion (Figure 1).

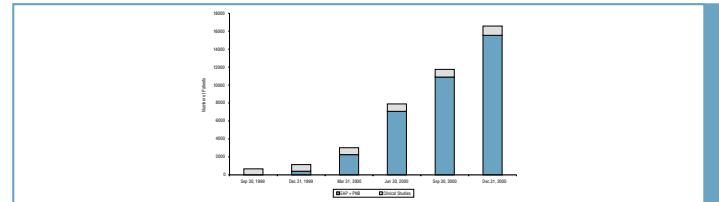
Figure 1. Scope of Kaletra Early Access Program



* Regulatory approval pending
Additional compassionate use programs were conducted in the following countries: Chile, Ireland, Luxembourg, Norway, and Sweden.

As of December 31, 2000 the overall enrollment in the Kaletra EAP was 11,679 patients, including 8,733 patients with confirmed dosing of Kaletra, from 847 investigators worldwide. At the time of FDA approval, approximately 11,740 patients were taking Kaletra worldwide, either through a clinical trial or compassionate use program, such as EAP or a patient named basis (PNB) program (Figure 2).

Figure 2. Cumulative Number of Patients Enrolled in Kaletra Programs



Challenges Addressed in Program

Due to the large scope of this EAP, implementation and management challenges were inevitable. The following is an abbreviated list of the challenges encountered to date.

- US and ex-US regulatory differences
 - The timeframe and required processes for review and approval of the EAP by Ethics Committees and Ministry of Health Organizations was different in each country resulting in staggered program start-up.
 - EAP was established as a Phase III clinical trial in some countries.

- Broad range of export/import regulations
 - Some countries require an import license for every shipment entering the country; therefore, several distribution centers were contracted and set up.
 - In order to export clinical drug outside of the US, several countries conducted the EAP under the US Investigational New Drug (IND) application. In general, the ex-US investigators were not always familiar with IND regulations and the required paperwork.
- Significant communication barriers
 - Documents were translated into more than 16 languages.
 - Local monitors were trained and required to be available.

METHODS

The objectives of this study were to make Kaletra available to HIV-infected patients through an EAP, and to obtain additional safety information on Kaletra in patients 12 years of age or older with confirmed HIV infection and AST/ALT <5 times the ULN at screening. Due to the nature of the EAP, limited safety and efficacy data were collected. Reporting of serious adverse events (SAEs) was required. Although routine clinical laboratory measurements (e.g., triglycerides, AST/ALT, glucose, etc.) were not collected as part of the EAP, recommendations for the monitoring of these parameters for subsequent patient management were included in the protocol. Sites were monitored by telephone on a monthly basis to verify the status of each patient enrolled at the site, to confirm an adequate clinical drug supply was available at the site, and to verify that all SAEs had been reported to the sponsor. Additional monitoring was conducted in accordance with local regulations. Study sites used local laboratories to assay plasma HIV RNA samples. Since not all study sites used the same HIV RNA assay, a cutoff of 500 copies/mL has been used to summarize study results. Approximately 6% of patients had baseline HIV RNA \leq 500 copies/mL. These patients were excluded from analysis of the efficacy data.

Due to initial drug supply limitations, enrollment was initially limited to patients with a CD₄ count \leq 50 cells/mm³ and HIV RNA \geq 10,000 copies/mL. However, after one month, the CD₄ criterion was increased to include patients with CD₄ count \leq 200 cells/mm³. In January 2000, clinical drug supply became more readily available, therefore, the CD₄ and HIV RNA criteria were eliminated entirely through a protocol amendment. Timing of implementation of the amended protocol varied due to differences in local regulatory requirements.

RESULTS

Summary of Demographic and Disease Characteristics

Screening information is available on 8,733 patients reported to have initiated dosing with Kaletra. The mean baseline HIV RNA and CD₄ count for these patients were 4.8 log₁₀ copies/mL and 167.5 cells/mm³, respectively. In addition, 61.7% of these patients had experienced at least one CDC Class C (AIDS-defining) event. Demographic and disease characteristics are presented in Table 1.

Table 1. Summary of Demographic and Disease Characteristics

Demographic or Disease Characteristic	(N=8733)	Demographic or Disease Characteristic	(N=8733)
Gender		CD₄ Count (cells/mm³) - Most Recent	
Male	86.3%	<50	32.1%
Race		50-200	37.7%
Caucasian	82.4%	>200	30.2%
Black	14.0%	Mean	167.5
Asian/Pacific Islander	1.5%	HIV RNA (copies/mL) - Most Recent	
Other	2.1%	\leq 500	6.4%
Age (years)		501-10,000	10.7%
Mean	41.4	10,001-100,000	38.2%
History of Hepatic Insufficiency		>100,000	44.6%
None	95.3%	Mean (log ₁₀ copies/mL)	4.8
History of Renal Insufficiency		Prior ARV Use (Mean)	
None	96.8%	NRTIs	4.7
CDC Classification		PIs	3.3
Asymptomatic	14.6%	NNRTIs	1.3
Symptomatic	23.6%		
AIDS-Indicator	61.7%		

As the inclusion/exclusion criteria for the Kaletra EAP were changed and implemented over time, the mean baseline status of the patient population shifted to less antiretroviral-experienced, healthier patients. Figure 3 displays the mean CD₄ cell count (most recent) at screening, while Figure 4 displays the mean number of prior NRTIs, PIs, and NNRTIs used prior to enrollment, demonstrating this change over time.

Figure 3. Mean CD₄ Cell Count for Patients Initiating Kaletra Therapy

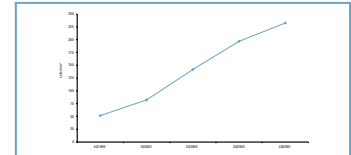
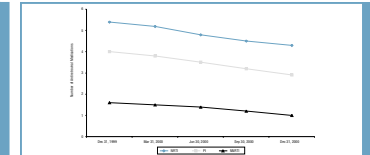


Figure 4. Mean Number of Antiretrovirals Used Prior to Initiating Kaletra Therapy



Viral Load Response Stratified by Baseline Characteristics

Plasma viral load measurements were evaluated as a function of baseline plasma HIV RNA (\leq 100,000 copies/mL, > 100,000 copies/mL), baseline CD₄ count (< 50 cells/mm³, 50-200 cells/mm³, >200 cells/mm³), prior NRTI use (0-2, 3-4, >4), prior PI use (0-2, 3, 4, 5), and prior NNRTI use (0, 1, >1). Also, the use of NNRTI as a new class was 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 log₁₀ copies/mL decrease from baseline (for those patients who did not achieve a measurement at or below 500 copies/mL). Results are summarized in Figures 5-10.

Figure 5. Percent of Patients with Viral Load Nadir \leq 500 copies/mL or \geq 1.0 log₁₀ Below Baseline Stratified by Baseline HIV RNA

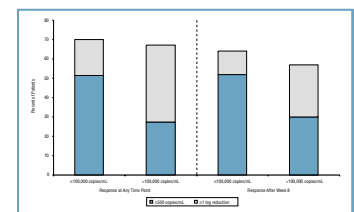


Figure 6. Percent of Patients with Viral Load Nadir \leq 500 copies/mL or \geq 1.0 log₁₀ Below Baseline Stratified by Baseline CD₄ Cell Count

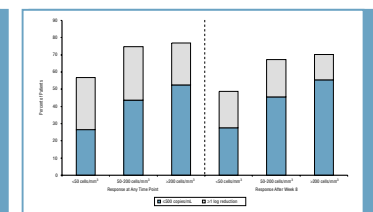


Figure 7. Percent of Patients with Viral Load Nadir \leq 500 copies/mL or \geq 1.0 log₁₀ Below Baseline Stratified by Prior NRTI Use

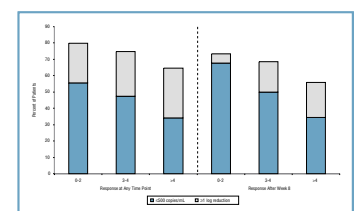


Figure 8. Percent of Patients with Viral Load Nadir \leq 500 copies/mL or \geq 1.0 log₁₀ Below Baseline Stratified by Prior PI Use

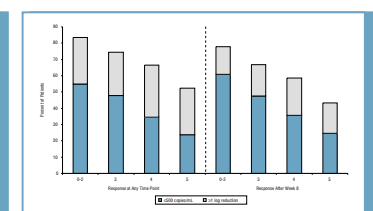


Figure 9. Percent of Patients with Viral Load Nadir \leq 500 copies/mL or \geq 1.0 log₁₀ Below Baseline Stratified by Prior NNRTI Use

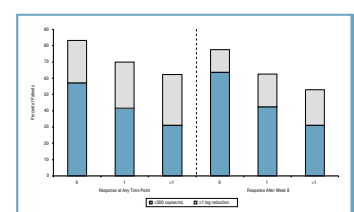
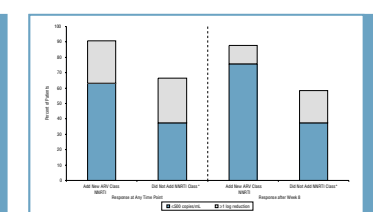


Figure 10. Percent of Patients with Viral Load Nadir \leq 500 copies/mL or \geq 1.0 log₁₀ Below Baseline Stratified by the Use of NNRTI as a New Class



Higher baseline viral load, lower baseline CD₄ cell count, and increasing number or prior NRTIs, PIs and NNRTIs were found to be associated with a significant decrease in viral load response. Also, the use of NNRTI as a new class was found to be associated with a significant increase in viral load response. Results from a univariate logistic regression analysis are presented in Table 2.

Table 2. Univariate Logistic Regression Analysis of Plasma Viral Load (Patients with Viral Load \leq 500 copies/mL or \geq 1.0 log₁₀ Decrease from Baseline)

	Response at Any Time Point Odds Ratio	95% CI	Response After Week 8 Odds Ratio	95% CI
HIV RNA	0.873	(0.771, 0.988)	0.742	(0.634, 0.868)
CD ₄	1.682	(1.544, 1.832)	1.671	(1.497, 1.865)
NRTIs	0.633	(0.562, 0.713)	0.611	(0.525, 0.712)
PIs	0.612	(0.573, 0.654)	0.613	(0.564, 0.667)
NNRTIs	0.629	(0.571, 0.693)	0.608	(0.538, 0.687)
Use of NNRTI as a new class	4.985	(3.406, 7.297)	5.122	(3.255, 8.062)

In general, all univariate factors (or their corresponding interaction effects) were determined to be statistically significant (p<0.05) in a multiple "stepwise" logistic regression analysis. (Note: The univariate factor, use of NNRTI as a new class, was not included in this analysis due to the potential confounding with the number of prior NNRTIs used.)

SAFETY RESULTS

A total of 8,733 patients were reported to have dosed in the Kaletra EAP through December 31, 2000. The disposition of these patients is summarized in Table 3.

Table 3. Summary of Patient Disposition*

	N
Subjects Dosed	8,733
Withdrew Consent	153
Adverse Event/HIV-Related Event	291
Death	155
Lost to Follow-up	228
Administrative	2743
Other	462

* Includes data collected through December 31, 2000; multiple reasons for the discontinuation of a given patient could have been specified.

Of note, three countries (France, Germany and the US) implemented closeout procedures for EAP and began supplying patients with Kaletra through other means by the end of December 2000. This accounts for the large number of discontinuations in the "administrative" and "other" categories.

Only serious adverse events (SAEs) were collected in the Kaletra EAP. No specific adverse event code was reported in greater than 1% of patients. The most common SAEs reported were fever (0.72%), pancreatitis (0.58%), pneumonia (0.56%), sepsis (0.40%), anemia (0.34%), and rash (0.27%). With the exception of rash, each of these SAEs were reported more frequently in patients with screening CD₄ counts <50 cells/mm³ when compared to patients with screening CD₄ counts \geq 50 cells/mm³ (p<0.001).

CONCLUSIONS

- With the inclusion of over 35 countries, the Kaletra early access program represents one of the largest antiretroviral expanded access programs to date.¹
- The mean baseline status of the patient population shifted over time to less antiretroviral-experienced patients as evidenced by the mean CD₄ count (51.7 versus 232.5 cells/mm³) and prior PI use (4.0 vs. 2.9) for patients enrolled during the fourth quarter 1999 and during the fourth quarter of 2000, respectively.
- The majority of the patients had a virologic response, with significantly higher response rates in patients who initiated therapy with low baseline viral load, high baseline CD₄, and less antiretroviral experience.
- No specific serious adverse event was reported in greater than 1% of the patient population.

ACKNOWLEDGMENTS

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REFERENCE

1. Beatty M, Cohen C, Coady W, Hellinger J, et al. Expanded access: the experiences of one research site. *Research Practitioner*, Volume 1, Number 5, 2000.