

sum, new product labeling is not warranted at this time for these hematologic events. This decision was based on the details of the cases, the calculated incidence rates from clinical trials and the expanded access program and review of the medical literature.

Incidence Rates of Serious Hematologic Events

	Clinical Trials: Incidence Rate	Expanded Access Program: Incidence Rate
Hemolytic Anemia	0	0.017% (2/11,800)
Thrombocytopenia	0.2% (2/897)	0.12% (14/11,800)
TTP	0	0.034% (5/11,800)

Rhabdomyolysis:

The applicant reported one event of rhabdomyolysis in phase 1-3 clinical trials (incidence rate 0.1% [1/897]) and 4 cases of rhabdomyolysis in the expanded access program (incidence rate 0.03% [4/11,800]). The case in the clinical trial database occurred in a patient following multiple traumas due to falls and pneumonia. In the expanded access program one case was seen in conjunction with hemolytic uremic syndrome with no apparent alternative etiology, another case occurred in a patient receiving cerivastatin and the third case was in a patient with pancreatitis. The fourth case appeared to be an abacavir hypersensitivity reaction by the investigator. During the postmarketing phase two cases were reported. In both cases patients were receiving statins.

No new labeling is recommended for rhabdomyolysis. The label clearly states the potential risk of rhabdomyolysis in patients receiving protease inhibitors and statins.

Renal Failure:

One case of renal failure was reported in the phase 1-3 clinical trials (incidence rate 0.1% [1/897]) and 25 cases were reported in the expanded access program (incidence rate 0.21% [25/11,800]). Fifteen of the 25 cases in expanded access program occurred in patients with a prior history of renal disease and the remaining 10 cases occurred in patients with significant degree of comorbidity or use of nephrotoxic medications. In addition, 4 reports of renal failure were seen during the postmarketing phase. Again these cases were observed in patients with severe comorbidity. No new labeling is recommended at this time for renal failure.

Hepatic Failure:

One event of hepatic encephalopathy was reported in a phase 1-3 clinical trial (incidence rate 0.1% [1/897]). This patient also had a history of hepatitis C infection and alcohol use and received concomitant isoniazid and methadone. A total of 19 cases of hepatic failure were reported in the expanded access program. All patients had comorbidities or received concomitant medications that possibly contributed to the event of liver failure. Eleven patients had a history of liver disease or hepatitis B/C, three patients were also receiving nevirapine, an agent which has been associated with severe hepatotoxicity. In addition, 4 cases of hepatic encephalopathy were reported in the expanded access program. Three of the events were fatal. All patients had a history of liver disease of hepatitis B/C infection or intercurrent infection that complicated the case.

Ten cases of hepatic failure were reported through the spontaneous postmarketing reporting system. Four reports described possible alternative etiologies and eight reports were in patients with hepatitis B or C infection or received concomitant hepatotoxic agents.

Based on these cases the PRECAUTIONS section: Hepatic Impairment and Toxicity, was revised to include the following information. The revised text is in bold type.

PRECAUTIONS:**Hepatic Impairment and Toxicity**

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment.

Review of Package Insert:

Please refer to 'Dr. Linda Lewis' review for labeling changes relating to the pediatric study 940.

In addition to the changes in the PRECAUTIONS: Hepatic Impairment and Toxicity section mentioned above, revisions were also made to the Microbiology, Description of Clinical Studies and Adverse Reactions section.

In the Microbiology section, information on the development of resistance from study 863 was included. Specifically, No evidence of resistance to KALETRA was observed in 37 evaluable KALETRA-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M mutation in HIV protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients.

Also updated information from study 957 on the impact of baseline genotype and phenotype on virologic outcome was included. Specifically, the 48 week virologic response (HIV RNA < 400 and < 50 copies) according to susceptibility and number of genotypic mutations at baseline in 50 evaluable patients enrolled in study 957 was presented in tabular format.

The Description of Clinical Studies was revised to include 48 week efficacy data from study 863. In addition the Adverse Reaction section was updated to include 48 week safety data from studies 863 and 957.

Kimberly Struble, PharmD
Senior Regulatory Review Officer
FDA/DAVDP

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Struble
2/13/02 11:38:49 AM
MEDICAL OFFICER

Debra Birnkrant
2/21/02 10:13:55 AM
MEDICAL OFFICER

CLINICAL REVIEW

Medical Officer's Review

NDA 21-251, SE8-004

Date of submission: July 12, 2001

Date received: July 13, 2001

Draft review completed:

January 18, 2002

Final review completed:

January 23, 2002

Reviewed by: Linda L. Lewis, M.D.
Medical Officer, HFD-530

Applicant: Abbott Laboratories
Pharmaceutical Products Division
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-6108

Drug name: Kaletra oral solution
(ABT-378/ritonavir, lopinavir/ritonavir)

Formulation: Co-formulated oral solution
(80 mg lopinavir/20 mg ritonavir per ml)

Indication: Treatment of HIV infection

Chemical structure:

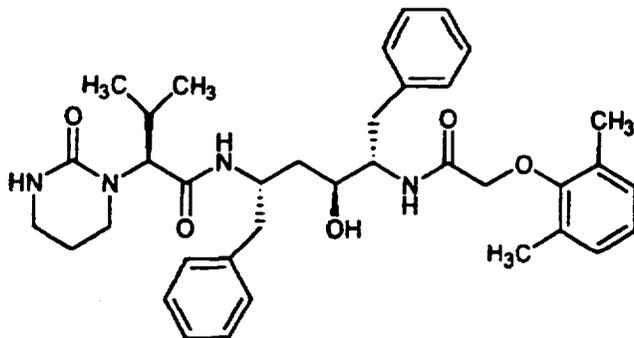


Table of Contents

Table of Contents..... 2

Executive Summary..... 5

I. Recommendations..... 5

A. Recommendation on Approvability.....5

B. Recommendation on Phase 4 Studies and/or Risk Management Steps5

II. Summary of Clinical Findings 6

A. Brief Overview of Clinical Program.....6

B. Efficacy6

C. Safety7

D. Dosing.....7

E. Special Populations.....8

Clinical Review 8

I. Introduction and Background 9

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor’s Proposed Indication(s), Dose, Regimens, Age Groups.....9

B. State of Armamentarium for Indication(s).....9

C. Important Milestones in Product Development10

D. Other Relevant Information10

E. Important Issues with Pharmacologically Related Agents10

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews..... 10

III. Human Pharmacokinetics and Pharmacodynamics..... 10

CLINICAL REVIEW

A.	Pharmacokinetics	10
B.	Pharmacodynamics	11
IV.	Description of Clinical Data and Sources	11
A.	Overall Data	11
B.	Tables Listing the Clinical Trials.....	11
C.	Postmarketing Experience	12
D.	Literature Review.....	12
V.	Clinical Review Methods.....	12
A.	How the Review was Conducted	12
B.	Overview of Materials Consulted in Review.....	13
C.	Overview of Methods Used to Evaluate Data Quality and Integrity	13
D.	Were Trials Conducted in Accordance with Accepted Ethical Standards.....	13
E.	Evaluation of Financial Disclosure.....	13
VI.	Integrated Review of Efficacy.....	13
A.	Brief Statement of Conclusions	13
B.	General Approach to Review of the Efficacy of the Drug.....	14
C.	Detailed Review of Trials by Indication.....	14
D.	Efficacy Conclusions	22
VII.	Integrated Review of Safety	22
A.	Brief Statement of Conclusions	22
B.	Description of Patient Exposure	22
C.	Methods and Specific Findings of Safety Review	23
D.	Adequacy of Safety Testing.....	34
E.	Summary of Critical Safety Findings and Limitations of Data	34
VIII.	Dosing, Regimen, and Administration Issues.....	35

CLINICAL REVIEW

IX.	Use in Special Populations	35
	A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation.....	35
	B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy.....	36
	C. Evaluation of Pediatric Program.....	36
	D. Comments on Data Available or Needed in Other Populations	37
X.	Conclusions and Recommendations.....	37
	A. Conclusions.....	37
	B. Recommendations.....	39

Clinical Review for NDA 21-251

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The supplement to NDA 21-251 (SE-8, 004) containing data from the extension of the pediatric clinical trial supports the indication for use of Kaletra in combination with other antiretroviral drugs for the treatment of HIV infection in patients over 6 months of age for up to 48 weeks. The supplement should be approved. Kaletra, in combination with other drugs, was found to be efficacious in reducing HIV viral load and increasing CD4 cell counts over the 48 week study period in both treatment naïve and treatment experienced children. No significant differences in response rate could be identified based on age or gender but children who had received prior therapy, especially those with previous protease inhibitor therapy, were more likely to fail therapy than treatment naïve children. The sponsor demonstrated an acceptable safety profile for Kaletra used in combination with other antiretroviral drugs. While adverse events were common in the study population, relatively few were considered possibly drug related, few were severe in nature or required discontinuation of study drug, and many were clearly related to common childhood illnesses or conditions. Clinically significant laboratory abnormalities were also relatively uncommon and rarely led to interruptions in the study regimen.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Kaletra has been shown to be very effective in treatment naïve pediatric patients. Efficacy decreases if children have had previous antiretroviral therapy and decreases most dramatically in those who have had prior therapy with other protease inhibitors (PIs). The U.S. HIV-infected pediatric population has a large proportion of children who have received multiple PIs and have few remaining treatment options. As part of their Phase 4 commitments the sponsor has agreed to evaluate the use of Kaletra in this population of more extensively treated pediatric patients, with special attention to identifying whether the currently approved dosing recommendations are adequate for children who have failed treatment with multiple (≥ 2) other PIs. The report for this study is anticipated in the July, 2004.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The pediatric development program for Kaletra will ultimately include study of all pediatric age groups. This submission reports the results of Study M98-940, a multinational, clinical trial of Kaletra oral solution in combination with other antiretroviral drugs for the treatment of HIV infection in patients 6 months to 12 years of age at the time of enrollment. One hundred patients were enrolled and stratified by age (< 2 years vs. \geq 2 years to 12 years) and by treatment history (treatment naïve vs. treatment experienced) at the time of enrollment. Treatment naïve patients received Kaletra plus stavudine and lamivudine as their study regimen while treatment experienced patients received Kaletra plus nevirapine and 1 or 2 nucleoside reverse transcriptase inhibitors. Patients were initially randomized to receive one of 2 doses of Kaletra, either 230 mg lopinavir/57.5 mg ritonavir or 300 mg lopinavir/75 mg ritonavir twice daily. After PK assessment all patients were given the higher dose and treated through the 48 week study period. Interim analysis of safety and efficacy was performed after 24 weeks and has been previously submitted and reviewed. This submission includes updated safety and efficacy data from the 48 week extension of Study M98-940.

B. Efficacy

Kaletra oral solution demonstrated good antiretroviral activity when used in combination with NRTIs over the 48 weeks of the study period. Overall, 75% of study patients achieved and sustained an HIV RNA level < 400 copies/mL and 66% reached an HIV RNA level < 50 copies/mL at Week 48. Among treatment naïve patients, 80% experienced a sustained virologic response (HIV RNA < 400 copies/mL) while treatment experienced patients had response rates of 71%. Among the treatment experienced patients, the subgroup who had received previous therapy with PIs had poorer response rates than those who had not received previous PI therapy. No differences in response rate could be identified based on age (< 2 years vs. \geq 2 years) or gender. All subgroups analyzed exhibited a significant decline in mean log HIV RNA levels over the 48 week study period with the whole study population achieving a mean decrease in viral load of 1.8 log. Additionally, significant improvements in CD4 cell counts were noted in all patient groups and subgroups. The CD4 responses were similar to viral load responses in that treatment naïve patients had a greater increase than did treatment experienced patients. These response rates are as good as or better than those achieved with other antiretroviral agents developed for use in children over the last several years.

C. Safety

Overall, the sponsor demonstrated an acceptable safety profile for Kaletra used in combination with other antiretroviral drugs in pediatric patients from 6 months to 12 years of age. While AEs were common among the 100 children in the study population, relatively few were considered possibly drug related. The most commonly reported events thought to be drug-related were vomiting, diarrhea, taste perversion (poor palatability), hepatomegaly and rashes. Moderate and severe events were identified in 38 children but in most cases the events represented some concomitant illness unlikely to be related to Kaletra. Hospitalizations and life-threatening events were almost entirely related to infectious complications such as pneumonia, viral infections or otitis media. Very few patients (7%) required interruption of their study drug dosing as a result of adverse events. Only a single patient was withdrawn from the study because of a presumed drug related serious adverse event (pancreatitis) and one patient died during the study period of causes unrelated to Kaletra use (Burkitt's lymphoma).

Similarly, there were relatively few clinically relevant laboratory abnormalities associated with Kaletra use in pediatric patients. The most commonly identified laboratory toxicities included elevated transaminases ($> 5 \times \text{ULN}$) in 7-8% of patients and elevated serum amylase ($> 2.5 \times \text{ULN}$) in 7%. No evidence of drug-related bone marrow suppression was found during the 48 week study. No new or unexpected toxicity was identified in the 48 week data that had not been previously identified during the review of the original 24 week data.

Some patients enrolled in the study were evaluated for phenotypic and genotypic resistance. Among children previously treated with PIs, 30% of those tested had evidence of reduced susceptibility to Kaletra (> 2.5 -fold increase in EC_{50} over wild type virus) at Baseline by phenotypic testing. No specific pattern of mutations in the protease gene could be correlated with this reduced susceptibility. No patients in the pediatric study developed new reduced susceptibility during treatment with Kaletra, consequently, it was not possible to identify any mutations predictive of phenotypic resistance. Of note, reduced susceptibility to Kaletra was not the only factor responsible for virologic failure in this population.

D. Dosing

Dosing for Kaletra oral solution was evaluated during the original NDA review. Nothing reported in the current submission warrants changing those recommendations for pediatric patients from 6 months to 12 years of age. The sponsor has agreed to evaluate dosing in heavily treatment experienced pediatric patients as one of their Phase 4 commitments.

E. Special Populations

Investigation of the use of Kaletra oral solution in all age groups has been requested in a formal Written Request dated 3/31/99 and amended 6/18/01. Studies in infants < 6 months of age and adolescents are currently in development. The current study provides adequate demonstration of Kaletra's efficacy in children 6 months to 12 years of age without evidence of differences related to gender or age group (< 2 years vs. ≥ 2years). Analysis of efficacy according to race/ethnicity was confounded by an imbalance in the number of black patients who were treatment naïve and treatment experienced. Studies in adult patients with hepatic impairment are being conducted and it is not considered necessary to repeat these studies in children.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review**I. Introduction and Background****A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

Kaletra (lopinavir/ritonavir, ABT-378/ritonavir) oral solution is a co-formulation of antiretroviral drugs in the class of HIV protease inhibitors (PIs). Lopinavir serves as the active antiretroviral compound while ritonavir serves, in this instance, as a pharmacologic enhancer by inhibiting the metabolism of lopinavir in the CYP3A system. The 2 drugs are administered in a co-formulation, either capsule or solution, at a fixed 4:1 ratio. Abbott Pharmaceuticals has submitted this efficacy supplement in support of labeling for pediatric usage in HIV-infected children from 6 months to 12 years of age. This submission includes updated 48-week safety and efficacy data from the single pediatric study, M98-940. The doses of Kaletra evaluated in the first 24 weeks of the study were 230 mg lopinavir/57.5 mg ritonavir BID (230/57.5 dose) and 300 mg lopinavir/75 mg ritonavir BID (300/75 dose). All subjects were escalated to the higher dose after interim evaluation of PK parameters (reported and reviewed in the original NDA) identified it as approaching most nearly the target exposure selected on the basis of adult pharmacokinetic/pharmacodynamic data. During the second 24-week period of the study (Weeks 24-48), the extension reported in this submission, all study subjects received the 300/75 dose.

B. State of Armamentarium for Indication(s)

Protease inhibitors have become the mainstay of highly active antiretroviral therapy when given in combination with nucleoside reverse transcriptase inhibitors (NRTIs). Combinations of 3 or 4 antiretroviral drugs are now standard therapy in North America and Europe and are gradually being adopted in more resource-poor countries as cost containment strategies are being implemented. The development of resistance to these agents continues and the need for new drugs with improved resistance profiles remains a critical need. Many of the currently available antiretroviral drugs also have significant adverse effects and drugs with better tolerability and toxicity profiles are also needed. Based on the 24-week data previously reviewed, it is anticipated that Kaletra has an acceptable safety profile and may have a resistance profile that allows its use in patients who have failed therapy with some other PIs.

C. Important Milestones in Product Development

The capsule and oral solution co-formulations of Kaletra have both been studied under IND — The adult Phase III treatment studies submitted under NDA 21-226 and the pediatric study submitted under NDA 21-251 were received in May, 2000 and reviewed simultaneously. Both the capsule and oral solution formulations of Kaletra were granted accelerated approval on the basis of 24-week data showing declines in HIV-1 RNA levels and improvements in CD4 cell counts over the 24-week study period. An efficacy supplement containing updated adult efficacy data for Kaletra was submitted to NDA 21-226 in March, 2001 and is currently under review. It is anticipated that the approval decision and any required labeling for the adult efficacy supplement and the review of the updated pediatric study data will be completed simultaneously so that a unified drug label for both formulations may be produced.

D. Other Relevant Information

None noted.

E. Important Issues with Pharmacologically Related Agents

None noted.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are no new clinically relevant findings from chemistry, pharmacology/toxicology or biopharmaceutics pertinent to this supplement. These data were reviewed in detail in conjunction with the original NDA. The current submission does contain some new virology data which has been reviewed by the Microbiology Reviewer, Dr. Julian O'Rear. Efficacy data has been evaluated by the Mathematical Statistics Reviewer, Dr. Rafia Bhore.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The original NDA 21-251 review contains a thorough discussion of the PK profiles obtained in children ages 6 months to 12 years. Because of the good safety margin and wide therapeutic range, dosing was converted from mg/m² BSA

dosing to mg/kg dosing, as it is more convenient and less subject to errors in calculation.

B. Pharmacodynamics

No pharmacokinetic/pharmacodynamic correlations are available for this relatively small pediatric population. There did not appear to be any differences in the efficacy of the 2 doses originally studied.

IV. Description of Clinical Data and Sources

A. Overall Data

This submission contains data from a single pediatric study, M98-940. The study was conducted by the sponsor and utilized 10 principal investigators in 6 countries. There was no additional data submitted from post-marketing surveillance, compassionate access protocols or from reviews of the literature.

This submission contains 23 volumes of material documenting the study results and Abbott's conclusions regarding Study M98-940, 48-Week Report. The paper copy is the official submission. In addition, a CD containing copies of the CRTs and CRFs has been submitted as a reviewer's aid. The CD contains datasets as SAS transport files of demographic, safety and efficacy data through 48 weeks. Comparisons of data from the reviewer's aid CD and the study report line listings supported the sponsor's assertion that the electronic datasets were a true representation of the data in the paper submission.

B. Tables Listing the Clinical Trials

Only a single trial is submitted for review, Study M98-940. Table 1 summarizes the patients enrolled by country and site.

Table 1: Subjects Enrolled in Study M98-940 by Site

Country	Number of Sites Enrolling	Number of Subjects Enrolled			Number Prematurely Discontinued
		Naïve	Experienced	Total	
Argentina	1	2	3	5	0
Bahamas	1	5	13	18	0
Canada	1	0	1	1	0
Panama	1	9	21	30	1
South Africa	1	27	0	27	1
United States	5	1	18	19	0

Only one (2%) of the enrolled subjects in the group of treatment naïve subjects was from a North American site, while there were 19 (34%) enrolled in the treatment experienced group from the U.S. and Canada.

Table 2 summarizes the disposition of all patients screened for the study at all sites.

Table 2: Disposition of Subjects in M98-940

Disposition	Number of Subjects
Total number screened	168
Did not meet entry criteria	44
Laboratory value exclusion	28
HIV RNA < 400 copies/mL at screening	16
Not randomized, study enrollment complete	10
Not randomized, other reasons*	10
Lost to follow-up prior to randomization	3
Withdrew consent prior to randomization	1
Randomized and received drug	100

*Includes additional "enrollment completed" subjects, unavailability of nevirapine oral solution

C. Postmarketing Experience

None submitted.

D. Literature Review

None submitted.

V. Clinical Review Methods

A. How the Review was Conducted

Study M98-940 was reviewed for both safety and efficacy. The sponsor's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. Dr. Rafia Bhore performed the statistical analysis confirming the primary endpoint and some secondary endpoints in the pediatric trial. This MO reviewed study design, patient demographics, adverse events and laboratory safety monitoring data and reviewed the efficacy results using the JMP Statistical Discovery software. In this review, tables that were derived from the sponsor's

presentation of the data are cited as to source in the table footnotes while those that are derived from reviewer-generated results are not referenced.

B. Overview of Materials Consulted in Review

The 23 volumes of material documenting the study results and Abbott's conclusions regarding Study 98-940, 48-Week Report were used as the primary data source in this review. No other data was reviewed.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Because of the relatively small number of patients enrolled in this study and the relative lack of subject drop-outs and missing data, no DSI audits were requested by the review team.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor states that the study was conducted according to accepted ethical standards based on the precepts established by the Declaration of Helsinki. A copy of a sample Informed Consent Form is included in the submission. The sponsor notes that it was the responsibility of the individual investigators to ensure that subjects and their legal guardians were given adequate information to assess the potential risks and benefits of study participation. There is no clear documentation of how this was evaluated for each site.

E. Evaluation of Financial Disclosure

The sponsor submitted financial disclosure information and this was reviewed in the original NDA package. Updated financial disclosure information was submitted for the 48 week study period. There were no new financial interests reported since the original NDA submission and review.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Kaletra oral solution exhibited good antiretroviral activity when used in combination with NRTIs over the 48 weeks of the study period. Overall, 75% of study patients achieved and sustained an HIV RNA level < 400 copies/mL and 66% reached an HIV RNA level < 50 copies/mL. Significant increases in CD4 cell counts and declines in mean log change in HIV RNA levels were noted in all patient groups analyzed. No significant differences in response rate could be identified based on age (< 2 years or ≥ 2 years) or gender but children who had received prior therapy, especially those with previous PI therapy, had poorer

responses than treatment naïve children. The response rates observed in Study M98-940 are as good as or better than those seen with other antiretroviral agents developed for use in children over the last several years.

B. General Approach to Review of the Efficacy of the Drug

HIV viral load as measured by HIV RNA PCR assays with a lower limit of quantitation (LOQ) of ~~—~~ copies/mL (standard Amplicor assay) or ~~—~~ copies/mL (Ultrasensitive assay) were used as the primary measure of efficacy. The proportion of patients who achieved and sustained a viral load below the LOQ was determined. The mean change in HIV RNA PCR (standard assay) from Baseline to Week 48 was calculated. Additionally, measurements of CD4 cell counts were reviewed and mean change from Baseline was determined for the analysis groups. Patients who were withdrawn from study prior to Week 48 because of adverse events or HIV-related illness were considered virologic failures and were included in the calculations of mean change in viral load and CD4 cell counts. The time to virologic failure endpoint was confirmed by the Statistical Reviewer.

C. Detailed Review of Trials by Indication

1. Summary of study design – Study M98-940

The study presented was a multi-center, open label, randomized trial of 2 doses of ABT-378/r in combination with nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-infected children. One hundred children between the ages of 6 months and 12 years were enrolled and randomized to receive either 230 mg ABT-378/57.5 mg ritonavir (Group 1) or 300 mg ABT-378/75 mg ritonavir (Group 2) given orally every 12 hours (later amended to be given BID). Patients were stratified at enrollment according to age (3 months to 2 years and 2 to 12 years) and prior treatment history (antiretroviral naïve or experienced). Patients naïve to antiretroviral therapy were given a regimen of Kaletra + stavudine (d4T) + lamivudine (3TC). Patients with prior antiretroviral therapy experience received a regimen containing Kaletra + nevirapine (NVP) + one or two NRTIs chosen by the local Principal Investigator.

Additional antiretroviral therapy was dosed as follows:
d4T - 1 mg/kg BID for subjects up to 30 kg, 30 mg BID for subjects weighing 30-60 kg, 40 mg BID for those weighing > 60 kg
3TC - 4 mg/kg BID to maximum dose of 150 mg BID for subjects 3 months through 11 years old, 150 mg BID for subjects > 12 years old

NVP – 4 mg/kg QD for the first 14 days, then 7 mg/kg BID for subjects 3 months to 8 years, 4 mg/kg BID for subjects > 8 years old
Doses of other NRTIs received by the experienced subjects were not specified in the protocol.

Pharmacokinetic sampling was performed on Day 21 of study and following analysis the higher of the 2 doses was selected for the continuation of the study based on prospectively defined criteria. All patients initially assigned to Group 1 were escalated to the higher dose between Study Days 82 and 141. During Weeks 24 through 48 all patients received the same dose of Kaletra. Consequently, the review for the extended 48 week data evaluates all patients together rather than comparing the 2 dose groups.

Study subjects were monitored monthly for safety and efficacy through the first 24 weeks then bimonthly from week 24 to week 48. Adverse events were recorded at each visit. Routine safety monitoring included: hematology studies (CBC, platelet count, PT/PTT), serum chemistries, thyroid panel, urinalysis, and serum pregnancy test (when appropriate). Measures of efficacy included: plasma HIV RNA PCR (as determined by a central laboratory using the Roche Amplicor assay and the Roche Ultrasensitive assay), CD4 and CD8 cell counts. In addition, samples were to be collected for viral genotype and phenotype from patients whose viral load remained > 400 copies/ml after the Week 24 visit (before any change in therapy). Uniform criteria were established for removal of study subjects from therapy and for study drug interruption and dose reduction.

Efficacy and safety assessments were conducted after all children enrolled in the trial had completed 24 weeks of study medications and again after participants had completed 48 weeks of study medications. Results of the first 24 weeks of study are described in the original NDA review. This review evaluates similar safety and efficacy measurements through 48 weeks of dosing. The endpoints for this phase of the study were time to loss of virologic response through Week 48 or the proportion of children with sustained viral load < 400 copies/mL Week 48, proportion of children with viral load < 50 copies/mL at Week 48, and change from baseline to Week 48 in virologic and immunologic variables.

The endpoint of time to loss of virologic failure was calculated according to a standard algorithm developed in the Division and shared with sponsors submitting NDAs for review. In brief this algorithm designates a patient as having a virologic response if he/she achieves at least 2 consecutive HIV RNA PCR values < 400 copies/mL (or < 50

copies/mL) at some time during the study and maintains that level through 48 weeks of study. The algorithm designates the time of virologic failure as: the first timepoint of at least 2 consecutive HIV RNA PCR values > 400 copies/mL (or > 50 copies/mL), the time of a patient death, or the time of discontinuation of study drug or addition of new therapy (substitutions of background NRTIs due to intolerance were permitted) after having first reached an undetectable viral load. Patients who never achieved at least 2 consecutive viral load values < 400 copies/mL were considered to have virologic failure from study Day 1.

For a more detailed analysis of the study procedures and identified protocol deviations, please see the MO review of the original NDA.

2. Study Population

One hundred children between the ages of 6 months and 12 years were enrolled after meeting the following criteria.

Inclusion criteria included:

- A confirmed diagnosis of HIV infection
- Viral load > 400 copies/ml
- Ability to take oral medications and comply with the protocol
- A parent or legal guardian able to provide informed consent

Candidates were excluded if they had:

- Past exposure to any non-nucleoside reverse transcriptase inhibitor
- Life expectancy < 12 months
- Any toxicity greater than > Grade 1
- Prior treatment with any investigational agent within 30 days
- Any active opportunistic infection or other clinically significant findings that would compromise the outcome of the study
- More than 2 episodes of moderate to severe diarrhea or vomiting not attributed to drug therapy lasting more than 4 days within 3 months of study
- Symptoms of encephalopathy or developmental delay that would reduce compliance
- Requirement for systemic chemotherapy

3. Study Population Baseline Characteristics

Subjects enrolled in Study M98-940 had the following baseline demographic and disease characteristics (see Tables 3 and 4).

Table 3: Demographic Characteristics of Study Subjects

Characteristic	All Enrolled Patients (N = 100)
Gender	
Male	43
Female	57
Age	
Mean (years)	5.3
< 2 years (N)	14
≥ 2 years (N)	86
Range	0.5-12.6
Race/Ethnicity	
Black	57
Caucasian	9
Hispanic	32
Mixed/Other*	2
Treatment History	
Naïve	44
Experienced (any ART)	56
Protease inhibitor	24

*The sponsor listing of Race/Ethnicity does not include a category "Mixed/Other" although their data-base clearly lists 2 descriptors for some children.

The majority of study participants who had received protease inhibitor (PI) therapy prior to enrollment in this trial had received a single PI (17/24, 71%) while relatively few had received multiple PIs (7/24, 29%). It was not possible to calculate the length of prior therapy for the patients enrolled in the study although the mean length of time since HIV diagnosis was 3.1 years for the study population.

**APPEARS THIS WAY
ON ORIGINAL**

Table 4: Baseline Disease Characteristics (mean)

	HIV RNA Level* (log copies/ml)	% Subjects with Baseline HIV RNA Level $\geq 10^5$	CD4 Cell Count (cells/ μ l)	CD8 Cell Count (cells/ μ l)
All Enrolled (N = 100)	4.67	39%	839	1512
Naïve (N = 44)	4.91	52%	920	1936
Experienced (N = 56)	4.48	29%	770	1179
Age < 2 years (N = 14)	4.73	43%	1765	2908
Age \geq 2 years (N = 86)	4.66	38%	694	1285

*Two patients had baseline HIV RNA PCR < 400 copies/ml.

4. Efficacy Results

In this study population the loss of virologic response was defined as the first occurrence of either 2 consecutive clinic visits with viral load measurements > 400 copies/mL using the standard HIV PCR assay or premature discontinuation from the study in a subject who had initially achieved a viral load < 400 copies/mL. The time to virologic failure was calculated from these data and presented in graphic format (Figure 1).

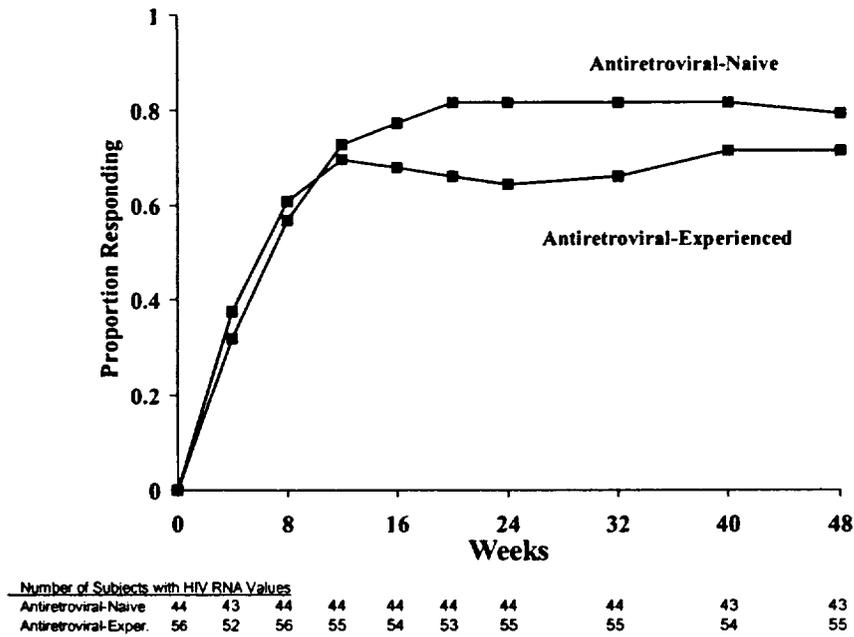
During the study, 75 participants had achieved and sustained a virologic response at the Week 48 visit. Thirty-five of 44 (80%) treatment naïve patients achieved sustained viral loads < 400 copies/mL while 40 of 56 (71%) treatment experienced patients had sustained virologic response. Of interest is the fact that several children did not reach a sustained level of HIV RNA PCR < 400 copies/mL until after 24 or more weeks of therapy with the study regimen.

Twenty-three study participants, 15 treatment experienced and 8 naïve, were considered treatment failures secondary to having 2 consecutive viral loads > 400 copies/mL. Thirteen of these patients had never achieved a sustained undetectable level of HIV RNA and 10 had rebound of viral load after achieving a virologic response. As noted above, virologic failure was more commonly identified in patients who were treatment experienced. Among patients who had previously received antiretroviral therapy, response rates to study therapy were lower in those children who had prior treatment that included PIs (16/24, 67%). Eight of the 13 patients who failed to reach a sustained virologic response were in the subset of patients who had received prior PI therapy.

Two children were considered treatment failures because they were discontinued from study prior to Week 48. One treatment experienced child was withdrawn from study because of an HIV-related event (Burkitt's lymphoma) and one treatment naïve child was withdrawn because of pancreatitis presumed to be study drug-related. The child who discontinued therapy after diagnosis of Burkitt's lymphoma had never achieved a virologic response while the child who developed pancreatitis while on study medication had undetectable viral load at the time of discontinuation.

The treatment response over the 48 week study period is displayed graphically in Figure 1 below reflecting the treatment outcomes reported in Table 5. Results from my analysis confirm the sponsor's results with regard to treatment outcomes and failure to sustain virologic response (< 400 copies/mL).

Figure 1: Treatment Response Over 48 Weeks in Study M98-940



(Figure source, Abbott Pharmaceutical, repeat virologic analysis provided in correspondence 12/14/01)

Table 5: Outcomes of Treatment in Study M98-940 through 48 Weeks

Outcome	All Patients (N = 100)	Treatment Naïve (N = 44)	Treatment Experienced (N = 56)
HIV RNA < 400 copies/mL	75 (75%)	35 (80%)	40 (71%)
HIV RNA > 400 copies/mL	23 (23%)	8 (18%)	15 (27%)
Rebound	10 (10%)	5 (11%)	5 (9%)
Never suppressed	13 (13%)	3 (7%)	10 (18%)
Death	0	0	0
Discontinued due to adverse events	2 (2%)	1 (2%)	1 (2%)*
Discontinued due to other reasons**	0	0	0

*This child had multiple adverse events leading to study drug interruption, ultimately was diagnosed with Burkitt's lymphoma, and was withdrawn from the study due to the lymphoma (an HIV-related illness).

**This category includes non-adherence, lost to follow-up, patient required prohibited medication, personal reasons, admission criteria violations and other similar reasons.

Because the Ultrasensitive assay for viral load was only performed at study visits from Weeks 32, 40 and 48, a rigorous analysis of time to virologic failure could not be performed using this assay. Sixty-six (66%) of the study patients had a viral load < 50 copies/mL at their Week 48 visit. An additional 14 patients had values between 50 and 400 copies/mL. There was little difference in the proportion of patients < 50 copies/mL in different subgroups. Thirty-one of the treatment naïve patients (70%) were undetectable using the Ultrasensitive assay while 35 treatment experienced patients (63%) were undetectable. The proportion undetectable by this assay was similar in children < 2 years and those greater than 2 years of age and in males and females. However, in the subset of treatment experienced patients who had received previous PI therapy only 13 of 24 (54%) reached an HIV RNA < 50 copies/mL at Week 48. Table 6 summarizes the proportion of patients who had viral loads below the LOQ for the 2 assays at their Week 48 visit. Of note, the proportion of children with viral load < 400 at the Week 48 visit is higher than the proportion who achieved and sustained an HIV RNA level < 400 (described above). The discrepancy is due to the few patients whose Week 48 HIV RNA values were < 400 although they had not been able to sustain those levels.

Antiviral activity can also be measured in terms of the change in a patients viral load while taking the study drug. The mean log change in viral load was calculated using the standard assay values available for children at Baseline and Week 48. As can be seen in Table 6, the study

CLINICAL REVIEW

population as a whole and all subgroups analyzed exhibited a significant decline in viral load over the course of the study. As might be expected, the treatment naïve patient group had the greatest response.

Table 6: Proportion of Study Subjects with Viral Load < 400 copies/ml, < 50 copies/ml and Log Change in Viral Load at Week 48 (Intent-to-treat)

	Proportion < 400 copies/ml at Week 48	Proportion < 50 copies/ml at Week 48	Mean Log Change in HIV PCR from Baseline to Week 48*
All Enrolled (N = 100)	79%	66%	-1.8
Naïve (N = 44)	84%	70%	-2.2
Experienced (N = 56)	75%	63%	-1.5
Age < 2 years (N = 14)	79%	64%	-1.9
Age ≥ 2 years (N = 86)	79%	66%	-1.8

*Calculation based on standard Roche Amplicor assay with LOQ ie child had missing Week 48 value (experienced, ≥ 2 years).

Similar calculations identified significant increases in CD4 cell counts during the course of the study. Table 7 shows the increases in CD4 cell counts from Baseline to Week 24 and Week 48 and the mean change over the study period. CD4 cell counts improved in all subgroups analyzed with greater increases observed in the treatment naïve group than the treatment experienced group. The patients < 2 years of age had smaller increases in CD4 cell counts than older children over 48 weeks but this may reflect their higher starting value and the natural decline in CD4 counts over the first few years of life.

Table 7: Mean Changes from Baseline to Week 48 for Absolute CD4 Cell Counts (cells/μl)

	CD4 Cell Counts at Baseline	CD4 Cell Counts at Week 24*	CD4 Cell Counts at Week 48*	Mean Change in CD4 from Baseline to Week 48
All Enrolled (N = 98)	846	1171	1182	335
Naïve (N = 43)	933	1249	1337	404
Experienced (N = 55)	779	1105	1060	282
Age < 2 years (N = 14)	1774	2200	1872	98
Age ≥ 2 years (N = 84)	692	1010	1067	375

* Calculations are based on number (N) of children with both baseline and Week 48 values. Four children had missing Week 24 values (all experienced, 3 children ≥ 2 years of age).

D. Efficacy Conclusions

Kaletra oral solution demonstrated good antiretroviral activity when used in combination with NRTIs over the 48 weeks of the study period. Overall, 75% of study patients achieved and sustained an HIV RNA level < 400 copies/mL and 66% reached an HIV RNA level < 50 copies/mL at Week 48. The subset of children who were treatment naïve at the time of study entry had the best response rates (80%) and treatment experienced children who had received previous therapy with PIs had the poorest response rate (67%). No differences in response rate could be identified based on age (< 2 years or ≥ 2 years) or gender. These response rates are as good as or better than other antiretroviral agents developed for use in children over the last several years. All subgroups analyzed exhibited a significant decline in mean log HIV RNA levels over the 48 week study period with the whole study population reaching a mean decrease in viral load of 1.8 log. Additionally, significant improvements in CD4 cell counts were noted in all patient groups and subgroups. The CD4 responses were similar to viral load responses in that treatment naïve patients had a greater increase than did treatment experienced patients.

VII. Integrated Review of Safety**A. Brief Statement of Conclusions**

Overall, the sponsor demonstrated an acceptable safety profile for Kaletra used in combination with other antiretroviral drugs in pediatric patients from 6 months to 12 years of age. While AEs were common in the study population, relatively few were considered possibly drug related and many were clearly related to common childhood illnesses or conditions. The most commonly reported events thought to be drug-related were vomiting, diarrhea, taste perversion (poor palatability), hepatomegaly and rashes. Similarly, there were relatively few clinically relevant laboratory abnormalities associated with Kaletra use in pediatric patients. The most commonly observed significant laboratory toxicities identified during the pediatric clinical trial included increased SGOT (8%), increased SGPT (7%), increased serum amylase (7%) and transient thrombocytopenia (4%). Only a single patient was withdrawn from the study because of a presumed drug related serious event (pancreatitis) and one patient died during the study period of causes unrelated to Kaletra use (Burkitt's lymphoma). No new or unexpected toxicity was identified during review of the 48 week study data that had not been previously identified during the review of the original 24 week data.

B. Description of Patient Exposure

The current report of Study M98-940 includes data from 100 children evaluated over a study period of 48 weeks. The duration of drug exposure for each patient

enrolled in the study reported in this submission ranged from 60 days to 378 days. Ninety-eight patients completed at least 336 days (48 weeks). Initially study participants were randomized to receive either 230/57.5 or 300/75 mg per m² BSA. After the interim analysis, all study patients received the higher dose for the duration of the study. Patients remaining on study at the end of 48 weeks continue to receive their assigned study medications and will be offered enrollment in a long term follow-up study sponsored by Abbott Pharmaceuticals.

C. Methods and Specific Findings of Safety Review

All 100 patients enrolled in Study 940 were included in the sponsor's safety analysis. Adverse events (AEs) were recorded for every patient at every study visit. Investigators at each site graded the intensity of the event (mild, moderate or severe) and the perceived relationship to study drug (not related, probably not related, possibly related or probably related). Serious adverse events (SAEs) were those events which resulted in: death, life-threatening situation, hospitalization, persistent or significant disability, congenital anomaly or other important medical event. AEs and SAEs were coded and compiled according to COSTART terms describing medical conditions. Laboratory studies including routine hematology and clinical chemistry studies were monitored at every visit. The safety analysis provided by the sponsor includes descriptive analyses of the compiled AEs and SAEs, evaluation of changes over time in laboratory tests and the occurrence of "extreme" (very high or low) laboratory values defined by the protocol. The sponsor's analysis and conclusions were confirmed by review of line listings and electronic datasets provided in the submission.

Adverse Events

Ninety-nine of the 100 children enrolled in Study M98-940 reported at least one AE during the 48 week study period. A total of 1186 AEs were reported during the study although in some cases multiple COSTART terms were listed describing the same event. For example, a single episode that included both vomiting and diarrhea might be coded as the 2 separate AEs "vomiting" and "diarrhea". Of the 1186 events, 1097 were graded as mild, 78 were graded as moderate and 11 were graded as severe in intensity. Of the total number of AEs, 771 were considered not related to study drug, 313 were considered probably not related, 26 were considered possibly related and 76 were considered probably related to study drug. Table 8 summarizes all AEs reported for Study M98-940 affecting > 10% of patients enrolled.

**Table 8: Adverse Events Reported Through 48 Weeks by 10% or More of Subjects
Regardless of Severity or Causality**

Body System/ COSTART Adverse Event	All Patients Enrolled (N = 100)
Body as a Whole	
Accidental injury	28%
Fever	36%
Headache	14%
Infection	52%
Viral infection	14%
Digestive System	
Diarrhea	30%
Gastroenteritis	19%
Vomiting	35%
Hemic and Lymphatic System	
Lymphadenopathy	11%
Respiratory System	
Asthma	11%
Bronchitis	13%
Cough increased	40%
Pharyngitis	58%
Pneumonia	13%
Rhinitis	40%
Skin and Appendages	
Eczema	21%
Fungal dermatitis	11%
Maculopapular rash	16%
Rash	27%
Special Senses	
Conjunctivitis	22%
Otitis media	39%
Taste perversion	22%

Source: M98-940 48-Week Report, Tables 12.2.a.

A majority of the AEs reported were thought to be unrelated to Kaletra use and of mild intensity. The most commonly reported events regardless of causality were those related to infections (eg., pharyngitis, rhinitis, otitis media) or gastrointestinal events (eg., vomiting, diarrhea, gastroenteritis). Many of these events are ones that would be frequently encountered in this age group, regardless of study participation. However, 21 of the 35 patients reporting vomiting had at least one episode of vomiting thought to be possibly or probably related to study

medication and one of these patients required a dose interruption. Many of these events were described as occurring with or after medication administration or due to Kaletra's poor palatability. Both vomiting and diarrhea have been ascribed to Kaletra use in studies conducted in HIV-infected adults.

One of the issues raised during the original NDA review of Kaletra oral solution was the relatively large proportion of ethanol in the formulation. The label contains a warning regarding the potential for ethanol overdose in smaller pediatric patients. No instances of Kaletra or ethanol overdose have been reported since the original review. Another potential toxicity related to the ethanol content of Kaletra oral solution is that of a disulfiram/ethanol interaction in children receiving metronidazole. During the study, 3 children received concomitant metronidazole for secondary infections. None of these children reported vomiting or other AEs associated with the simultaneous administration of metronidazole and Kaletra.

Unlike the adult studies which utilized Kaletra capsules, the pediatric trial studied the oral solution which has been reported to have an unpleasant taste. It is unclear whether the poor taste is due to the lopinavir component or the ritonavir component or both. Ritonavir oral solution is notorious among pediatric clinicians for its extremely poor palatability. The sponsor attempted to track this as an adverse event primarily using the COSTART term "taste perversion". Twenty-two children reported complaints of bad or bitter drug taste, although poor palatability was not responsible for any patients discontinuing therapy. All of these events were considered probably related to study medication. Most of the AEs in this category were reported from the study site in South Africa where study patients might not be exposed to as many medications during childhood as children in the U.S. or Europe. Possibly the investigator at this site was more diligent in reporting this non-medical complaint. While patient complaints that a drug tastes bad rarely have any medical significance they do have a tremendous impact on drug acceptance and adherence, especially in pediatric patients. Rarely, poor palatability can lead to vomiting significant enough to cause dehydration or other clinically relevant events. As noted above, some patients in the study had vomiting associated with medication administration, although no child was withdrawn from the study because of poor palatability, vomiting or refusal to take Kaletra.

Rashes were also described in many children participating in this study. Rash events were described using a variety of COSTART terms including: rash, maculopapular rash, and hypersensitivity reaction/allergic reaction. Rash or maculopapular rash was reported in 36 children and allergic reactions including rash was reported in one. In all likelihood, some of the reported rashes may have been due to other medications given during the study, particularly nevirapine given as part of the regimen for treatment experienced patients. Twenty-four of the 37 patients reporting rash AEs were treatment experienced children who

CLINICAL REVIEW

received nevirapine as part of their study treatment. Some of these reported events were described as insect bites, dermatitis, diaper rash, viral infection or other events unlikely to be related to study medications. Four children required study medication dose interruptions because of their rash AEs.

When evaluating all events considered at least possibly related to study drug the most commonly reported were taste perversion (22), vomiting (21), diarrhea (12), hepatomegaly (5) and rashes (5). Of the 1186 AEs reported, very few were felt to be possibly or probably related to study drug and of moderate or severe intensity. Nine patients reported 15 events that were thought to be drug related and at least moderately severe. These events are listed in Table 9 below. The only AE considered at least possibly related to study drug and at least moderate in severity that occurred in > 2% of the study population was rash, occurring in 3 patients (2 receiving concomitant nevirapine). The more severe rash AEs are highlighted in the table.

Table 9: Adverse Events Reported Through 48 Weeks Considered to be Possibly or Probably Related to Kaletra and at least Moderate in Severity

Subject Number	Onset of Event (days)	Event Description (COSTART term if different)	Severity of Event	Relationship to Study Drug as Determined by Investigator
203	22	Constipation	Moderate	Possible
206	141	SGPT increased	Moderate	Probable
302	238	Pancreatitis	Severe	Possible
313*	2	Viral infection	Moderate	Possible
	3	Dry skin	Moderate	Possible
	3	Rash	Moderate	Possible
	4	Hepatomegaly	Moderate	Possible
331	133	Vomiting	Moderate	Probable
405	23	Dislikes taste of ABT-378/r (taste perversion)	Moderate	Probable
428	54	Hypersensitivity reaction with fever, rash, jaundice (allergic reaction)	Moderate	Probable
431**	48	Eye swelling, vomiting, abdominal pain and arthralgia	Moderate	Probable
	64	Increased bilateral eye swelling with cellulitis	Moderate	Possible
447*	10	Fever	Moderate	Probable
	10	Rash	Moderate	Probable

*Subject 313 had multiple events listed over a 3-day period that were all part of the same illness. Subject 447 had 2 events that occurred on the same day as part of the same illness.

****Subject 431 was later found to have Burkitt's lymphoma and later AEs were thought to be due to that HIV-related event.**

HIV-related Events

During the 48 week study period, 14 children experienced HIV-related events. One of these events, an HIV-related Burkitt's lymphoma resulted in the death of a study patient (see case summary in Deaths section below). Four other HIV-related events were considered of moderate severity while the remaining episodes were considered mild. Other HIV-related events included 4 children with oropharyngeal candidiasis, 3 children with chronic ulcers > 1 months duration (all herpes simplex), 3 children with herpes zoster, and 1 child each with herpes simplex at other sites, other candidiasis and recurrent pneumonia. Eight of the children with HIV-related events were treatment naïve while 6 were treatment experienced. No specific pattern of events was apparent.

Serious Adverse Events

The sponsor reported that serious adverse events (SAEs) occurred in 21 patients during the 48 weeks of the clinical trial. Medical Officer review identified 22 patients with at least one reported SAE. One of these SAEs (Subject 431, lymphoma) resulted in patient death and one child had an event that was considered life-threatening (Subject 201, asthma and pneumonia) while all others were considered SAEs on the basis of requiring hospitalization. As can be seen in Table 10, several children required more than one hospitalization during the study period and most of the SAEs reported were thought to be unrelated to study drug. No specific pattern of SAEs could be attributed to use of Kaletra.

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

Table 10: Serious Adverse Events Reported Through Week 48

Subject Number	Onset of SAE (days of treatment)	Event Description (COSTART term if different)	Severity of Event	Relationship to Study Drug (Investigator)
102	56	Pneumonia, right basal	Mild	Not related
	116	Pneumonia, right	Moderate	Not related
	216	Bronchopneumonia (recurrent pneumonia)	Mild	Not related
106	9	Dacryocystitis (infection bacterial)	Mild	Not related
107	22	Bilateral pneumonia	Severe	Not related
	22	Chronic otitis media	Severe	Not related
201	42	Wheezing (asthma)	Mild	Not related
	210	Pneumonia	Severe	Not related
205	272	Gastroenteritis	Mild	Not related
207	377	Otitis media	Moderate	Not related
302	95	Pneumococcal sepsis with reactive arthritis (sepsis)	Severe	Not related
	238	Pancreatitis	Severe	Possibly
308	90	Dysentery (bloody diarrhea)	Severe	Probably not
324	188	Gastroenteritis	Severe	Probably not
402	26	Viral syndrome (infection viral)	Severe	Probably not
410	60	Infected burns (infection)	Moderate	Not related
417	229	Diarrhea	Mild	Not related
418	237	Croup (laryngitis)	Mild	Not related
422	27	Otitis media	Moderate	Not related
428	50	Varicella (infection viral)	Moderate	Not related
431*	33-93 (multiple events)	Hypersensitivity reaction	Moderate	Probable
		Cellulitis left leg	Mild	Not related
		Burkitt's lymphoma	Severe	Not related
		Echthyma gangrenosum	Severe	Not related
432	148	Spastic diplegia needing hamstring release surgery (reaction unevaluable)	Mild	Not related
434	54	Otitis media with perforation	Moderate	Not related
	56	Impetigo (infection bacterial)	Moderate	Probably not
436	338	Fractured femur (accidental injury)	Moderate	Not related
438	71	Viral syndrome	Moderate	Probably not
	126	Viral syndrome	Mild	Probably not
	126	Serous otitis media	Mild	Probably not

CLINICAL REVIEW

442	69	Fever	Moderate	Probably not
	69	Cough (cough increased)	Moderate	Probably not
	69	Rhinitis	Moderate	Probably not
443	22	Bullous impetigo (infection)	Moderate	Not related
	326	Herpes zoster	Moderate	Not related
	366	Headache	Mild	Not related
	366	Transient blindness	Mild	Not related

*After the diagnosis of Burkitt's lymphoma, all SAEs reported for Subject 431 were thought secondary to the lymphoma. It is probable that even the earliest events attributed to study drug represented undiagnosed lymphoma.

Interruptions of Study Medications

There were only 7 patients who required interruption in their study drug regimen during the 48 week study period. One patient had study drug temporarily interrupted because of vomiting study medications. Four patients had study drug interrupted secondary to rash events and later successfully restarted study regimen. Three of the 4 patients with rashes that prompted study drug interruption were treatment experienced patients receiving nevirapine while one was treatment naïve. In all 3 of the treatment experienced patients, rash was attributed to use of nevirapine in combination with Kaletra. Only 2 patients whose study drugs were interrupted went on to permanently discontinue Kaletra, Subject 431 diagnosed with Burkitt's lymphoma and Subject 302 who developed pancreatitis. A summary of Subject 431 can be found in the following section describing deaths during the study.

Subject 302, a 6 year old boy, was noted to have elevated amylase prior to baseline but had no symptoms of pancreatitis. Study regimen with Kaletra, d4T and 3TC was begun on 8/17/99. Study drugs were interrupted on 9/11/99 after both serum amylase and pancreatic amylase were elevated to 274 U/L and 106 U/L respectively. Over the next several weeks the subject was followed and laboratory values returned to normal. He remained asymptomatic throughout this time. A regimen of Kaletra, d4T and abacavir was restarted on 10/26/99. The investigator's opinion was that the event was probably not related to study drug but might be related to use of 3TC. On 3/38/00 he was reported to have serum and pancreatic amylase levels of 328 U/L and 309 U/L. He developed abdominal pain with elevated pancreatic enzymes and abnormal physical exam and was admitted to the hospital 4/11/00. All study drugs were discontinued at that time and he was treated with intravenous antibiotics and made NPO. Abdominal ultrasound revealed a "slightly bulky" pancreas but no pseudocyst. The child improved clinically within a few days and amylase levels decreased over several weeks but remained above the normal level. It was decided to discontinue the subject from the study. The investigator considered the second episode of pancreatitis possibly related to Kaletra but also possibly related to either d4T or abacavir.

Deaths

One patient died during the 48 week study period. Subject 431 was prematurely discontinued from study on Day 93 after being diagnosed with Burkitt's lymphoma. The subject was a 6 year old boy with a history of prior antiretroviral therapy who initiated 230/57.5 mg Kaletra plus stavudine, nevirapine, abacavir and didanosine on 8/30/99. He was escalated to 300/75 mg Kaletra on Day 85 of study. Prior to study discontinuation he had been hospitalized several times for illnesses that were initially diagnosed as hypersensitivity reaction (Days 33 and 48), eye swelling and cellulitis (Day 65), leg cellulitis (Day 66), and finally vomiting, dehydration and bone pain (Day 85). He was treated with a variety of medications including antibiotics, diuretics and systemic and inhaled steroids. Study drug was interrupted from Day 43 through Day 76. At the time of his last hospitalization before diagnosis of lymphoma he was found to have bilateral proptosis, multiple enlarged lymph nodes and liver and spleen enlargement. Bone marrow biopsy confirmed the diagnosis of Burkitt's lymphoma. The subject received antineoplastic therapy, study treatment and supportive care. Complications of his course included GI bleeding and thrombocytopenia, fever with neutropenia, oral herpes and candidiasis. All study drugs were permanently discontinued on 11/30/99 (Day 93) and he died a few weeks later after developing echthyma gangenosum and sepsis. In retrospect his earlier AEs and hospitalizations were thought to be due to undiagnosed lymphoma and all hospitalizations and death were considered unrelated to study medications. However, the sponsor did not retrospectively change the AE/SAE database and the original event was listed as probably drug related.

Laboratory Abnormalities

The sponsor's analysis of clinical laboratory data evaluated mean changes from baseline, shift in toxicity grade, number of subjects with "extreme" (very high or very low) laboratory values, and laboratory abnormalities experienced as AEs or requiring intervention. These analyses were reviewed and confirmed by the Medical Officer.

For the whole study population, statistically significant mean changes in several hematologic variables were noted during the study period. There were small mean increases in basophils, lymphocytes, neutrophils, total WBCs, MCV, MCHC and hemoglobin over 48 weeks. Number of RBCs and prothrombin time decreased slightly from baseline. There were also several clinical chemistry parameters that were statistically significantly different from baseline during the study period. Consistent increases in creatinine, sodium, chloride, albumin, alkaline phosphatase, cholesterol and triglycerides were noted. Consistent decreases in phosphorus, total protein, SGOT/AST, LDH and serum amylase were also noted. None of these mean changes were considered clinically relevant although the changes in cholesterol (mean increase of 40 mg/dL) and triglycerides

CLINICAL REVIEW

(mean increase of 23 mg/dL) may have implications for long term therapy. Some of the changes may represent known HIV drug-associated processes (MCV, cholesterol, triglycerides) while some changes may represent the normal physiologic changes that occur as children grow (creatinine, alkaline phosphatase, LDH). It is impossible to separate these etiologies since they may be occurring simultaneously in any given patient.

Another way of evaluating the safety data is to determine the number of children who had laboratory values outside of some pre-defined "extreme" values. The sponsor identified very high and very low values for hematology and clinical chemistry variables. For some of the variables the sponsor's protocol-defined extreme values (usually equivalent to Grade 3 toxicity) were too liberal and the criteria were modified after the initial NDA review. The numbers of patients developing the modified extreme laboratory values are summarized in Table 11 shown below and are reflected in the product label. As can be seen from the table, very few patients had critically elevated or depressed laboratory parameters.

Table 11: Numbers of Subjects with Extreme Laboratory Values through Week 48

Very High Laboratory Variables	Indicator Criteria	Number of Patients (N = 100)
Uric Acid	> 12.4 mg/dL	1
Sodium	> 149 mEq/L	3
Potassium	> 6.4 mEq/L	1
Calcium	> 11.9 mg/dL	1
Total Bilirubin	> 3 x ULN	3
SGOT	> 180 U/L	8
SGPT	> 215 U/L	7
Cholesterol	> 300 mg/dL	3
Triglycerides	> 750 mg/dL	1
Amylase	> 2.5 x ULN	7
Prothrombin time	> 2.33 x ULN	1
Very Low Laboratory Variables		
Sodium	< 130 mEq/L	3
Potassium	< 2.5 mEq/L	1
Hemoglobin	< 7 g/dL	1
Neutrophils	< 0.4 x 10 ⁹ /L	2
Platelets	< 50 x 10 ⁹ /L	4

ULN = upper limit of normal value

Source: Study M98-940 – 48 Week Report, Statistical Table 14.3.4_2.3.1, 2.3.2, 3.3.1, 3.3.2

Among the most frequently observed extreme laboratory values were those for SGOT, SGPT and amylase. Almost one third of the children enrolled in the study had modest elevations of SGOT and/or SGPT at some time point but only 7-8% had markedly elevated liver transaminases ($> 5 \times \text{ULN}$) during the course of the study. Two children with extreme transaminase levels were noted to have "hepatitis" as an AE at the time of their increased transaminases, Subject 308 described with "viral infection, hepatitis A" and Subject 336 also with "hepatitis A".

Total serum amylase is frequently elevated in children with salivary gland hyperplasia, a common condition among HIV-infected children. While it was not the study routine for children to be tested for pancreatic amylase, many of the children with significantly elevated total serum amylase were evaluated with this assay. Most of the children with serum amylase $> 2.5 \times \text{ULN}$ who were tested with the confirmatory assay did have elevated pancreatic amylase, but at relatively low levels. Only Subject 302 who had clinical pancreatitis had significantly elevated pancreatic amylase. While several patients had elevated serum amylase levels and mildly elevated pancreatic amylase levels, these abnormalities did not appear to predict the development of symptomatic pancreatitis.

Although there was no significant change in mean platelet counts over time in the study population, there were 4 children who developed extreme thrombocytopenia during the study period. Three of these children had a single recorded platelet count at Week 3 of $< 50 \times 10^9/\text{L}$ with both baseline and re-test values in the normal range. No intervention was performed in these subjects and the significance of these isolated values is unclear. The additional patient with thrombocytopenia was Subject 431 who developed Burkitt's lymphoma.

Three children were observed to have elevated cholesterol levels during the study. While it must be remembered that these values represent non-fasting cholesterol levels, at least one of the children (Subject 335) appeared to have progressively higher cholesterol during the 48 week study period. In Subject 406, almost all cholesterol values were in the abnormal range with several values $> 300 \text{ mg/dL}$. It is likely that a demonstrable impact of Kaletra on cholesterol levels, a PI class-related toxicity, may increase as the drug is used over longer periods of time, but this common adult toxicity is, in general, observed less frequently in children.

Resistance to Kaletra in Children

Twenty PI experienced patients had baseline isolates tested for HIV genotype and phenotype. Baseline resistance profiles were correlated with treatment outcome at 24 or 48 weeks. In a different analysis, 23 patients (5 naïve, 9 NRTI experienced/PI naïve and 9 NRTI and PI experienced) who experienced loss of virologic response had baseline isolates tested for phenotype and genotype with

22 of these having follow up testing at Week 24 and/or Week 48 after viral rebound (HIV RNA > 400 copies/mL). Viral phenotype was determined using the ~~1~~ HIV assay (~~1~~). Sequencing of the protease and reverse transcriptase genes from patient isolates identified mutations in amino acid sequence compared to a standard laboratory strain of HIV.

Of the 20 treatment experienced patients who had genotypic and phenotypic resistance testing done at baseline, 6 had reduced susceptibility to Kaletra defined as ≥ 2.5 -fold change in EC_{50} compared to wild type HIV. Nine children exhibited ≥ 2.5 -fold reduced susceptibility to at least one PI and 10 children displayed decreased susceptibility to at least 2 NRTIs. While the numbers are small, the proportion of children achieving virologic response at either Week 24 or Week 48 was less in those with > 10-fold change in EC_{50} (1/3, 33%) compared to those with 2.5-10-fold change (2/3, 67%). It appears that treatment outcome may be correlated with the cumulative number of mutations identified in the protease gene sequence, but no specific pattern of mutations determined at baseline can accurately predict response or lack of response. In this study a significant number of children with no measurable reduction in baseline isolate susceptibility failed to achieve a virologic response (6/14) substantiating the idea that emergence of resistance is not the only reason for virologic failure.

Twenty-three patients had HIV isolates tested for emergence of resistance after experiencing viral rebound after 24 and/or 48 weeks of study therapy. None of the 5 treatment naïve patients developed phenotypic reduced susceptibility to Kaletra (> 2.5-fold increase in ED_{50}), although there were 2 patients with mutations identified in the protease gene (L10I and L63L/P). Four of these 5 patients did develop the M184I/V mutation associated with lamivudine resistance. Similarly, none of the 9 NRTI experienced/PI naïve patients developed reduced susceptibility or mutations in the protease gene (genotyping available in 8 children). Six of the 8 children developed mutations in the reverse transcriptase region associated with NNRTI resistance (K101E, K103N and Y181C) and were shown to have reduced susceptibility to nevirapine. Among the 9 NRTI and PI experienced children tested at baseline and after rebound, 3 exhibited reduced susceptibility to Kaletra and mutations in the protease sequence that were present at baseline. Three additional patients developed new mutations during therapy (L10I and G73S) but these were not associated with changes in susceptibility compared to baseline. Another patient had a mutation (L33F) that was accompanied by a further reduction in his baseline reduced susceptibility. Isolates from all patients in this NRTI and PI experienced group developed new phenotypic resistance to nevirapine accompanied by new mutations in the reverse transcriptase region associated with NNRTI class resistance. Because so few new protease mutations emerged and no new phenotypic resistance was identified in this very small cohort of children, no specific pattern of mutations could be identified that predicted loss of susceptibility to Kaletra over time.

D. Adequacy of Safety Testing

Safety monitoring performed during this study was considered adequate and commensurate with that performed in conjunction with other studies of antiretroviral drugs in children. In younger children and infants smaller volumes of blood are used for assessing hematology and clinical chemistry parameters.

E. Summary of Critical Safety Findings and Limitations of Data

Overall, the sponsor demonstrated an acceptable safety profile for Kaletra used in combination with other antiretroviral drugs in pediatric patients from 6 months to 12 years of age. While AEs were common among the 100 children in the study population, relatively few were considered possibly drug related. The most commonly reported events thought to be drug-related were vomiting, diarrhea, taste perversion (poor palatability), hepatomegaly and rashes. Local investigators may have little incentive to assign causality for AEs to a study drug that represents a source of funding for their site but in this case many of the AEs were clearly illnesses and events that occur frequently in children. Moderate and severe events were identified in 38 children but in most cases the events represented some concomitant illness unlikely to be related to Kaletra. Hospitalizations and life-threatening events were almost entirely related to infectious complications such as pneumonia, viral infections or otitis media. Very few patients (7%) required interruption of their study drug dosing as a result of adverse events. Only a single patient was withdrawn from the study because of a presumed drug related serious adverse event (pancreatitis) and one patient died during the study period of causes unrelated to Kaletra use (Burkitt's lymphoma). The adverse event that may have the most impact on actual use of Kaletra was not a medical condition at all but the frequent complaints of its unpalatable taste.

Similarly, there were relatively few clinically relevant laboratory abnormalities associated with Kaletra use in pediatric patients. Significant SGOT and SGPT elevations were seen in 8% and 7% of patients and Grade 3 total bilirubin was documented in 3%. At least 2 of the patients with marked transaminase levels were noted to have concomitant hepatitis A. Serum amylase elevations were also seen in 7% of patients but in all but one of these cases the levels were already in the abnormal range at study Baseline. A small number of children had transient thrombocytopenia (4%) and neutropenia (2%) but after reviewing the study population as a whole there was no indication of drug-related bone marrow suppression. No new or unexpected toxicity was identified in the 48 week data that had not been previously identified during the review of the original 24 week data.

Some children with HIV isolates that exhibited reduced susceptibility to Kaletra were identified during this study. Six of 20 PI-experienced patients tested at Baseline had reduced susceptibility to Kaletra but resistance could not be correlated with a specific pattern of mutations. The development of resistance to Kaletra during therapy was not identified in this relatively small pediatric study. While a few patients exhibited new mutations in the protease gene, these did not seem to correspond to reduced susceptibility. Only one child who had reduced susceptibility at Baseline had a further reduction during the 48 week study period.

There are very few limitations to the safety data reviewed and these are relatively minor. There is no indication from the current study that there are any differences in safety according to age or race. However, the number of children under the age of 2 years was relatively small and may not have provided a complete picture of toxicity in this age group. It was not possible to determine whether there might be differences in the safety profile according to race/ethnicity since this data was confounded by the disproportionate number of blacks enrolled who were treatment naïve and the relatively small number of non-Hispanic Caucasians. The number of children with reduced susceptibility to Kaletra was too small in this study to draw any conclusions regarding the association of a specific pattern of mutations with phenotypic resistance.

VIII. Dosing, Regimen, and Administration Issues

Dosing recommendations for HIV-infected children using Kaletra in combination with other antiretroviral drugs have not changed since the original NDA was reviewed and approved. Please refer to the original NDA review for a discussion of the approved dosing regimen for children \geq 6 months of age to 12 years of age.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Study M98-940 had an adequate number of children of both genders enrolled to provide adequate safety and PK data. The sponsor identified no differences in toxicity or efficacy based on gender. There were not enough children enrolled in the study to fully evaluate potential differences in efficacy in both treatment naïve and treatment experienced patients based on gender. Previous antiretroviral therapy was the major determinant of response in the pediatric population studied. The sponsor's evaluation of gender in this study is felt to be adequate as there are no data from other studies of HIV therapy in the pediatric population to suggest a difference in response to therapy or toxicity according to gender.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor conducted analyses evaluating efficacy, safety and PK profile in children 6 months to 2 years of age (N = 14) compared to those 2 to 12 years of age (N = 86). No differences were found in any of the safety parameters evaluated. Antiviral activity was not discernibly different in the younger and older children with similar proportions reaching and sustaining an undetectable viral load in the 2 age strata. The younger children did have a less marked increase in CD4 cell counts over the course of the study. This may have been due to the natural decline in CD4 cell counts that occurs in children in the first few years of life and is not thought to represent a lack of efficacy in the younger age group. Data are not available in adolescents.

This study was conducted at sites in North and South America, Africa and the Caribbean. In all 57% of the study population was black and 32% was Hispanic. The proportion of patients with viral load < 400 copies/mL at Week 48 according to race/ethnicity ranged from 65% in Hispanics (20/32) to 86% in blacks (49/57) and 89% of Caucasians (8/9). These data are confounded by the disproportionate number of the black children who were treatment naïve and a corresponding disproportionate number of Hispanic children who were treatment experienced. Treatment history was the most important determinant of response identified in the study. These data do not support a difference in efficacy based on race or ethnicity but this may be an area that would benefit from further study.

C. Evaluation of Pediatric Program

This study of 100 HIV-infected children treated with Kaletra oral solution in combination with other antiretroviral drugs has provided adequate PK, safety and efficacy data for approval of the drug for use in children > 6 months old. Both treatment naïve and treatment experienced children were evaluated. This submission provides useful information regarding the durability of treatment response over 48 weeks in this population. It is probable that this study will be used when the sponsor submits final study reports for a determination of pediatric exclusivity. To date, the use of Kaletra has not been studied in infants < 6 months of age or in adolescents (approximate age group 12-16). A request for safety and PK data in both of these age groups has been made in the form of a Pediatric Written Request issued to the sponsor on 3/31/99 and amended on 6/18/01. These data were requested to be submitted no later than 7/1/04.

D. Comments on Data Available or Needed in Other Populations

The data contained in this supplement and the original NDA submission show that Kaletra is a potent antiretroviral drug with an acceptable PK profile and safety profile. It had demonstrable activity in the subset of patients who had received previous therapy with PIs, although the response was not as robust as in less treatment experienced or naïve patients. Study of the drug in children who have failed multiple other PIs, possibly at higher doses, may yield important information regarding the use of Kaletra in salvage therapy regimens. Collection of information regarding the patterns of resistance leading to lack or loss of response to Kaletra will be important in this population.

It is also important to study Kaletra in infants < 6 months old. This is a population for which there are fewer treatment options currently available. An easily administered, potent PI would be of great benefit for HIV-infected patients in this age group.

X. Conclusions and Recommendations

A. Conclusions

The accelerated approval of Kaletra oral solution in Sept., 2000, provided pediatric patients with an age-appropriate formulation of a new protease inhibitor that appeared to be tolerable, safe and effective in a 24 week clinical trial. The current submission provides extended safety and efficacy data through 48 weeks of therapy, still a relatively short period in the scope of life-long HIV therapy, that confirms those initial findings. The longer term data suggest that the safety and tolerability issues identified in the original review remain but no new issues have been identified.

Kaletra, in combination with other drugs, was found to be effective in reducing HIV viral load and increasing CD4 cell counts over the 48 week study period in both treatment naïve and treatment experienced children. This conclusion is based on analysis of HIV RNA and CD4 cell count data from Study M98-940, the Phase 3 pediatric clinical trial. The 48 week study report contained data for the entire study period from 98 of the initially enrolled 100 study patients. For this analysis, the efficacy endpoint was the more rigorous one of sustained undetectable viral load rather than simply recording an undetectable level at the 48 week visit. Overall, 75% of the study's participants achieved and sustained through 48 weeks an HIV RNA level < 400 copies/mL. Eighty percent of treatment naïve pediatric patients achieved a sustained response while 71% of treatment experienced patients were sustained responders. As might be expected, pediatric patients who had previously received other PIs were less likely to respond but even in this population approximately two-thirds of patients achieved a sustained response. When the analysis used the more sensitive LOQ of the

CLINICAL REVIEW

Ultrasensitive assay, the proportion reporting an undetectable HIV RNA decreased in all groups with an overall rate of 65% reporting < 50 copies/mL at Week 48.

Similarly, increases in CD4 cell counts could be documented in all stratified groups and subgroups analyzed. It was noted in the original review that the study population had well-preserved CD4 cell counts at the time of study entry. Over the second half of the study CD4 cell count increases were maintained in the study population. After 48 weeks of study medications including Kaletra, treatment naïve children had a mean increase of 404 CD4 cells/mm³ while treatment experienced patients experienced a mean increase of 282 CD4 cells. Children < 2 years of age appeared to have a less robust CD4 response than older children. From the available data it is unclear whether this represents decreased efficacy in this age group or the natural decline in CD4 cell counts that occurs over the first few years of life.

In general, the tolerability and safety profile of Kaletra was acceptable and similar to that observed in the adult studies. While the most common drug related complaint was poor palatability, this issue did not result in interruption of study medications or premature discontinuation from study. Vomiting, diarrhea, hepatomegaly and rashes were the most commonly reported clinical conditions attributed to study medication. Most of these events were mild and self-limited. Adverse events led to interruption of study drug in 7 children in the clinical trial but most tolerated re-challenge. Of note, 3 of the 4 children with more severe rashes were treatment experienced patients who were also receiving nevirapine. Only 2 patients were discontinued from the study prematurely, one because of presumed drug-associated pancreatitis and one because of an HIV-related event (Burkitt's lymphoma) that resulted in death. Many of the adverse events and serious events reported were clearly related to secondary infections commonly observed in children with HIV infection.

Routine laboratory monitoring during the study revealed very few clinically relevant abnormalities. SGOT and SGPT values greater than 5 x ULN were identified in 8% and 7% of the study participants over the 48 week study period and serum amylase levels greater than 2.5 x ULN were observed in 7% of patients. The prevalence of these laboratory abnormalities did increase between the 24 week interim report and the 48 week final study report but occurred at approximately the same rate during the 2 periods of the study. A few children experienced transient thrombocytopenia and/or neutropenia but evaluation of the entire study population revealed no evidence of significant bone marrow effects that might be drug-related.

This submission also contained information regarding the presence at baseline or emergence during study of phenotypic resistance to Kaletra or mutations in the protease gene. Among children who had received previous PI therapy, 6 of 20 studied had reduced susceptibility to Kaletra at Baseline. Although an increasing

number of protease gene mutations was correlated with decreasing susceptibility, no specific mutation or pattern of mutations predictive of resistance could be identified. Development of new phenotypic resistance could not be identified in a subset of patients who were studied at Baseline and at Week 24 or Week 48 after suffering virologic rebound. Emergence of new mutations in the protease gene during therapy was rare and not correlated with reduced susceptibility. Clearly, in this pediatric population virologic failure was related to other factors (such as adherence) in addition to drug resistance.

The pediatric study of Kaletra in combination with other antiretroviral drugs for the treatment of HIV infection in pediatric patients 6 months through 12 years provides evidence of acceptable safety and tolerability and good antiviral activity over 48 weeks of treatment. Infants < 6 months of age and adolescents have not been studied at this time but the sponsor notes that protocols including these age groups are in development in collaboration with the ———. Results of these studies will provide additional useful information in the most appropriate use of Kaletra in the pediatric population. The sponsor has also agreed to evaluate the use of Kaletra in pediatric patients with more extensive previous PI therapy and to determine whether the currently approved dose is appropriate in this subpopulation (Phase 4 commitment). Continued monitoring of adverse events, laboratory abnormalities and emergence of resistance will proceed in on-going and future pediatric and adult studies.

B. Recommendations

This supplement to NDA 21-251 (SE8, 004) containing 48 weeks of data from the extension of the pediatric clinical trial supports the use of Kaletra in combination with other antiretroviral drugs for the treatment of HIV infection in patients 6 months to 12 years of age. The supplement should be approved pending receipt of the final revised label and agreement by the sponsor to the Phase 4 commitments related to this submission and to NDA 21-226. Submission of studies in infants < 6 months and in adolescents has been deferred until July, 2004. Studies defining the use of Kaletra oral solution in all pediatric age groups, from neonates to adolescents, have been requested in a formal Written Request issued 3/31/99 and amended 6/18/01.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Linda Lewis
1/24/02 05:40:50 PM
MEDICAL OFFICER
Supplement approved 1/18/02

Jeffrey Murray
1/25/02 01:17:35 PM
MEDICAL OFFICER

Debra Birnkrant
2/5/02 02:48:37 PM
MEDICAL OFFICER