CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226

21-251

MEDICAL REVIEW

Medical Officer's Review
NDA 21-251, SN 000

Date of submission: May 31, 2000
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Applicant: Abbott Laboratories
Pharmaceutical Products Division
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-6108

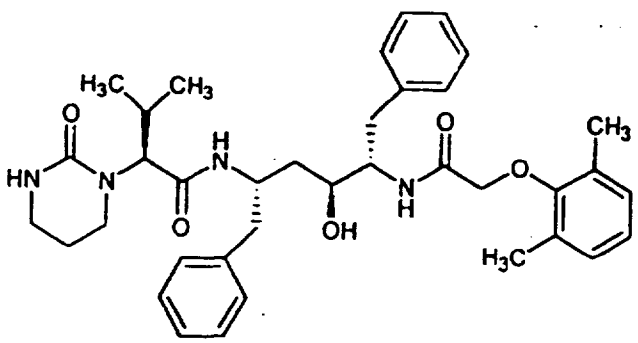
Drug name: ABT-378/ritonavir, lopinavir/ritonavir

Trade name: Kaletra

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

Proposed indication: Treatment of HIV infection in children

Chemical structure:



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1.0 Resume

This application contains pharmacokinetic, safety and preliminary efficacy data from a single pediatric clinical trial, Study M98-940, in support of the approval of co-formulated lopinavir/ritonavir (ABT-378/r) oral solution in the treatment of HIV infection in children. The study was a multi-national, open-label, randomized trial of two doses of ABT-378/r (Group 1 at 230 mg/57.5 mg or Group 2 at 300 mg/75 mg) in combination with other antiretroviral agents. Patients were stratified at entry according to prior antiretroviral therapy (naïve or experienced) and age at enrollment (3 months to 2 years and 2 to 12 years). Pharmacokinetic (PK) sampling was performed to include patients in all strata. After preliminary analysis of the PK data, the 300/75 dose level was selected for further study and all subjects were subsequently dosed at this level. Efficacy and safety data through 24 weeks of study have been analyzed by the sponsor and submitted in the M98-940 Study Report and these data have now been evaluated by a Division of Antiviral Drug Products review team. ABT-378/r provides good antiretroviral activity in pediatric HIV patients and appears to have an acceptable safety profile. The NDA should be approved for use in children between 6 months and 12 years of age with minor modifications to the proposed drug label as indicated below.

2.0 Introduction and Regulatory Background

ABT-378 (lopinavir) is a novel peptidomimetic HIV protease inhibitor with in vitro potency greater than 10-fold that of ritonavir. When given alone the PK profile of the drug revealed relatively rapid metabolism that would have required frequent dosing. Using the information that the drug is metabolized by the CYP3A4 system, the sponsor identified significantly improved PK parameters when ABT-378 was coadministered with ritonavir, a potent CYP3A4 inhibitor. Initial studies in adults were performed with coadministration of the separate drug products. These studies investigated several dose combinations of the 2 drugs in both PK and preliminary efficacy studies. The combination of 400 mg ABT-378 and 100 mg ritonavir resulted in an acceptable profile of PK, safety and tolerability, and preliminary efficacy. This ratio was reproduced in the co-formulated capsules and subsequently in the oral solution.

The capsule and oral solution co-formulations of ABT-378/r have both been studied under IND —— The capsule is currently under review in NDA 21-226 submitted simultaneously with this application. Much of the preclinical data and the chemistry and manufacturing information related to this NDA have been previously submitted and are reviewed along with NDA 21-226. They will not be reviewed here unless specific to the oral solution. The sponsor plans to describe both formulations in a single patient package insert. This review will comment only on the parts of the drug label specific to the oral solution and pediatric usage.

Abbott Laboratories submitted with this application the required certification and disclosure of financial interests and arrangements with clinical investigators (Form FDA

3454 and Form FDA 3455). Three investigators for M98-940 disclosed significant financial arrangements and interests with the sponsor, either as equity interest in Abbott Laboratories or payments received for another clinical trial. These investigators enrolled a total of 7 subjects out of the 100 children who participated in M98-940 and their participation is not considered to bias the outcome of this study.

3.0 Materials Submitted

This submission includes the integrated summaries of safety and efficacy for previous adult clinical trials of ABT-378/r and the detailed study report for M98-940, the single pediatric clinical trial. The full submission includes 30 volumes, 18 of which contain clinical/statistical information examined by this reviewer. At the time of submission the pediatric expanded access program had just opened and no data from this program was available for review. Conclusions regarding efficacy and safety are, therefore, based on the 100 pediatric patients reported in study M98-940. No new data from adult patients receiving the oral solution are reported other than from those enrolled in the bioequivalence studies reported with the pharmacokinetic data.

3.1 Reviews of Non-clinical Material by Other Disciplines

3.1.1 Chemistry

Chemistry, manufacturing and controls issues have been reviewed for both the capsule formulation and the oral solution by Dr. Ko-Yu Lo. Please see her review for general information regarding the chemical synthesis and manufacturing specifications. One issue that seems particularly relevant to the use of the solution formulation in children is the requirement for relatively large amounts of ethanol as a solvent/excipient. In recent years the American Academy of Pediatrics has urged pharmaceutical manufacturers to decrease or remove ethanol from pediatric formulations. For the protease inhibitors this has been difficult because of serious limitations in the solubility of the compounds. The proposed market formulation contains 356 mg ethanol/ml of ABT-378/r (42.4% v/v). This amount of ethanol used in the formulation would give the equivalent of 89-106 mg/kg/day (depending on dose), a dose of ethanol well above most currently marketed formulations for children.

Reviewer's comments:
While the amount of ethanol in this formulation may seem excessive when compared to other chronically used medications, the potential benefits of a highly effective antiretroviral agent may outweigh this concern. As a comparison, ritonavir oral solution contains 370 mg ethanol/ml (43% v/v) and has been used successfully in children of all ages (approved for use in children > 2 years). The package insert for ritonavir carries only a

precaution/warning not to use the drug in combination with disulfiram or metronidazole because of possible adverse interactions. For this product, a more informative statement regarding the amount of ethanol a child might ingest should be included since the sponsor seeks approval for use in children as young as 6 months.

4.0 Study M98-940 – Pediatric Clinical Trial

4.1 Protocol Description

4.1.1 Study Objectives

The study objectives included: 1) determination of an adult-equivalent dose of ABT-378/r in HIV-infected children based on the PK profile and the tolerability of the drug in combination with NRTIs and 2) characterization of the safety and antiviral efficacy of ABT-378/r in combination with NRTIs.

4.1.2 Protocol Design

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 3 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 ABT-378/r + stavudine (d4T) + lamivudine (3TC, 4 mg/kg BID to maximum dose of 150 mg BID). Patients with prior antiretroviral therapy experience received a regimen containing ABT-378/r + 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.

As described below, PK 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.

Study subjects were monitored monthly for safety and efficacy. 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 Roche Amplicor 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.

4.1.3 Study Population

One hundred children between the ages of 3 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

The study was conducted at sites in:

Panama (30 subjects)
South Africa (27 subjects)
Bahamas (18 subjects)
United States (19 subjects)
Argentina (5 subjects)
Canada (1 subject)

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.

4.1.4 Protocol Procedures

Protocol defined PK studies were performed at Day 21 and preliminary analysis of this data was used to select the final dose for study. PK sampling was to be performed on the first 20 subjects between 2 and 12 years of age enrolled at each of the dose levels and the first 8 subjects < 2 years of age at each dose level. The final study dose was to be selected based on prospectively defined criteria; that it resulted in < 20% of subjects experienced Grade 3 or 4 toxicity or laboratory abnormality, > 75% of subjects achieved ≥ 0.5 log decrease in HIV RNA PCR at Week 3, and "central" values for AUC and C_{min} between 80-130% of the average adult exposure. In the event that both dose levels met these criteria, the dose that yielded central PK parameters closest to 100% of the average adult exposure would be selected. After the preliminary PK analysis the 300/75 mg dose fulfilled these criteria and all study subjects receiving the lower dose were escalated to 300/75 mg at Weeks 12 to 16.

4.1.5 Protocol Deviations

The sponsor identified a number of protocol deviations, some of which may have had some impact on the study results. The sponsor notes that there were no deviations from the protocol enrollment criteria. However, one patient was noted in the study report to have a viral load of < 400 copies/ml at screening but had a value > 400 at baseline and was allowed to enroll (unable to determine subject number). Two patients (#104 and #311) not mentioned in the study report had baseline viral loads of < 400 copies/ml after having screening values of 7817 and 847 copies/ml respectively and were allowed to begin study. These 2 subjects had no other viral load values > 400 throughout the study.

Although the sponsor states that no subjects were enrolled who did not meet the clinical laboratory criteria, there were also a number of study subjects whose baseline values for clinical laboratory studies exceeded the

protocol criteria (any toxicity > Grade 1). For example, 2 patients had baseline values for SGPT that were > 2 times the upper limit of normal (x ULN), 3 patients had baseline values for SGOT > 2 x ULN, and 18 patients had total amylase levels > 1.4 x ULN with 2 of these children having repeat pancreatic amylase levels also greater than Grade 1 toxicity.

There were a small number of randomization errors during patient enrollment that were identified in the database. Two treatment-experienced patients were randomized (to dose level) as naïve and one naïve patient was randomized as experienced.

There were several errors in dosing procedure during the study. At one site (#14711), 18 subjects did not have their study drug doses adjusted for changes in body surface area until approximately Day 80. Eighteen treatment experienced patients (sites #14711 and #14684) did not start NVP on Day 1 as the protocol requires. Thirteen of these patients at site #14711 were given the naïve regimen of ABT-378/r, d4T and 3TC rather than the NVP containing regimen until Day 22. After being switched to the NVP regimen at Day 22, these patients were inadvertently left on the QD lead-in dose of NVP rather than the full BID dose until 100-114 days into the study.

Reviewer's comments:

The randomization errors and deviations from clinical laboratory enrollment criteria represent relatively minor protocol violations. It is unlikely that the subjects who were randomized incorrectly adversely affected the study conclusions. However, patients enrolled with baseline elevated clinical laboratory values did contribute to the proportion of patients who were identified as having Grade 3 or 4 toxicity during the course of the study.

The enrollment of patients who had baseline levels of HIV RNA < 400 copies/ml may have had more impact on the results of the study. Neither of these subjects had any HIV RNA levels above the limit of quantitation and so were counted as treatment successes. There is no information available suggesting whether the reported screening values for these patients represent a transient blip in an otherwise stable undetectable viral load or whether there may have been other therapeutic changes in the relatively recent past that might have led to a declining viral load at the time of study entry. While enrollment of these 2 patients may lead to an overestimation of the primary endpoint efficacy, it is unlikely that it would have a major impact on interpreting the success of the regimen.

It is possible that the incorrect dosing of study drugs in 18 of 51 treatment-experienced subjects, especially NVP, may have had an impact

on assessing study regimen efficacy. If these patients had previously received either 3TC or d4T (or both), they may have been receiving a suboptimal regimen for the first 3 weeks of study. Many were then underdosed with NVP, receiving only ½ the appropriate dose for the next few months. The effects seen in this group of subjects may underestimate the efficacy of the drug regimen but also reflect the potency of ABT-378/r as the remaining highly active agent.

4.2 Study Results

4.2.1 Patient Demographics

One hundred and sixty-eight patients were screened to enroll 100 study subjects. Of the 68 who were not enrolled, 28 patients were not eligible because of disqualifying screening laboratory values, 16 had screening viral load < 400 copies/ml, 14 were not randomized because the study had already filled, 3 were lost to follow-up before enrollment, 1 withdrew consent before randomization and 6 "failed for other reasons" including an unavailability of NVP solution at one site.

One hundred patients were randomized and dosed according to protocol (see above protocol deviations). Forty-nine were randomized to Group 1 (230/57.5) and 51 were randomized to Group 2 (300/75). Tables 1 and 2 list the baseline demographic and disease characteristics of children enrolled in the study. The randomized study groups were well-matched according to the stratifications for age and prior treatment history. Of the 14 children who were < 2 years of age, 5 subjects were less than 12 months old and 9 were between 12 and < 24 months old.

Table 1: Demographic Characteristics of Study Subjects

Characteristic	All Enrolled Patients (N = 100)	Group 1 Patients (N = 49)	Group 2 Patients (N = 51)
Gender			
Male	43	22	21
Female	57	27	30
Age			
Mean (years)	5.3	5.5	5.1
< 2 years (N)	14	6	8
≥ 2 years (N)	86	43	43
Range	0.5-12.6	0.5-12.6	0.5-11.9
Race/Ethnicity			
Black	56	28	28
Caucasian	9	6	3
Hispanic	32	13	19
Mixed/Other*	3	2	1
Treatment History			
Naïve	44	22	22
Experienced	56	27	29

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

Of the 56 children enrolled in the study who had received prior antiretroviral therapy, 52 had received zidovudine, 49 had received lamivudine, 15 had received didanosine, 15 had received abacavir, 11 had received stavudine and 1 had received zalcitabine. Only 24 had received another protease inhibitor prior to the study. Twenty-one of the 24 had received ritonavir, 6 had received nelfinavir, 5 had received saquinavir and 2 had received indinavir. Most of the protease inhibitor experienced subjects had received only one PI (17 of 24).

Table 2: Baseline Disease Characteristics (mean)

	HIV RNA Level* (log copies/ml)	Baseline HIV RNA Level $\geq 10^5$	CD4 Cell Count (cells/µl)	CD8 Cell Count (cells/µl)
All Enrolled (N = 100)	4.67	39%	839	1512
Group 1 (N = 49)	4.79	47%	816	1540
Group 2 (N = 51)	4.55	31%	862	1486
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 ≥ 2 years (N = 86)	4.66	38%	694	1285

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

4.2.2 Pharmacokinetic Determinations and Dose Selection

The pharmacokinetic data was reviewed in detail by Drs. Prabhu Rajagopalan, Jooran Kim and Kellie Reynolds and their assessment is included in this NDA review package. A summary of the sponsor's PK report is included here. Pharmacokinetic sampling was performed on 56 subjects (53 reported) on Day 22 over a period of 12 hours. Levels of both ABT-378 and ritonavir were measured and PK parameters were determined for both drugs. As expected, the doses of ritonavir administered in this co-formulation gave drug exposures that were well below the therapeutic levels for that agent. Initial analysis of the PK data suggested that the 300/75 mg dose level provided ABT-378 exposure closest to the pre-determined target (see Table 3) and this dose was selected as the final study dose.

Table 3: Pharmacokinetic Parameters for ABT-378 after Administration of ABT-378/ritonavir

	AUC_{12} (μg•h/ml)	C_{max} (μg/ml)	C_{min} (μg/ml)
Dose 1 - 230/57.5 mg/m^2 q12h			
All subjects (N = 26)	61.3	7.38	2.52
Subjects < 2 years (N = 5)	62.1	8.00	2.14
Subjects > 2 years (N = 21)	61.1	7.23	2.64
Dose 2 - 300/75 mg/m^2 q12h			
All subjects (N = 27)	102.8	11.38	5.21
Subjects ≤2 years (N = 7)	81.0	9.97	2.99
Subjects > 2 years (N = 20)	110.4	11.87	5.98

Source: M98-940, Appendix 16.1.13 (Drug Metabolism Report), page 32.

Further analysis also revealed a significant interaction between ABT-378/r and NVP (see Table 4). (Those study subjects who inadvertently received an incorrect NVP regimen were analyzed as not receiving the drug in the final PK analysis.) While the lower dose studied in M98-940 gave drug exposures that were similar to those identified in the successful adult clinical trial, the addition of NVP to that regimen decreased ABT-378/r exposure by a significant amount. When combined with NVP the dose of 230/57.5 mg produced drug exposures of ABT-378/r that were lower than those produced with the chosen adult dose. The higher dose of 300/75 mg gave exposures of ABT-378/r that were significantly above the adult target exposure when given without NVP. Again, combination of the higher dose ABT-378/r with NVP significantly decreased exposure to ABT-378/r giving levels that were similar to the adult target exposure.

Table 4: Pharmacokinetic Parameters of ABT-378 Administered as ABT-378/ritonavir with or without Nevirapine (NVP) Compared to Adult Exposures

	AUC_{12} (μg•h/ml)	C_{max} (μg/ml)	C_{min} (μg/ml)
Dose 1 - 230/57.5 mg/m^2 q12h			
With NVP	51.6	6.71	1.80
Without NVP	72.6	8.16	3.35
Dose 2 - 300/75 mg/m^2 q12h			
With NVP	85.8	10.04	3.56
Without NVP	116.4	12.45	6.53
Adults - 400/100 mg*	77.4	8.94	3.46

*Weighted means from Study M97-720 and M97-765 – Week 3-4.

Source: M98-940, Appendix 16.1.13 (Drug Metabolism Report), page 37.

The sponsor has chosen the higher dose of 300/75 as the optimal dose to be marketed for children. The sponsor believes that this dosing recommendation allows the concomitant use of NVP if needed and demonstrates no added toxicity compared to the lower dose of ABT-378/r.

The sponsor has conducted studies in adults to evaluate the effect of food on absorption of ABT-378/r. These studies are summarized in the material submitted for this NDA. For both the capsule and oral solution formulations, bioavailability was increased significantly by administration of the drug with food. The food effect was relatively greater for the solution than the capsule resulting in an 80% increase in AUC and 54% increase in Cmax when given with a moderate fat meal relative to fasting. These increases are greater when the drug is taken with a high fat meal. In order to enhance bioavailability and reduce PK variability the sponsor recommends that ABT-378/r be taken with food.

Reviewer's comments

It is not entirely clear that the 300/75 mg/m^2 dose of ABT-378/r represents the optimal dose for all pediatric patients. This dose provides exposures similar to the adult exposures when given with NVP but exceeds these levels by approximately 50% when not given with NVP. While this study revealed no statistically significant dose-related increase in toxicity at the higher dose there were numerically slightly more cases of diarrhea reported at the higher dose and no apparent increase in efficacy. The lower dose of 230/57.5 mg/m^2 provides adequate exposures and similar activity when not given in combination with NVP. There is, however, some data from the adult clinical trials suggesting that heavily pre-treated patients receiving ABT-378/r plus efavirenz (which decreases ABT-378 concentrations by approximately 30%) may have had a better response when given a higher dose of ABT-378/r (533/133 mg). Since perinatal transmission in the U.S. has declined dramatically in the last few years, most of the children eligible to receive this drug are likely to be treatment experienced and might theoretically benefit from the higher dose.

There has also been debate regarding the optimal method of dosing children, ie., mg/m^2 of body surface area (BSA) or mg/kg of body weight. While most health care providers prescribing antiretroviral agents for children are familiar with calculating doses based on BSA, there is common concern that more dosing errors occur because of these calculations and inaccuracies in measuring height (or length) in young children. In the absence of a significant pharmacologic reason to use one method over the other, most pediatricians and pediatric nurses would prefer the mg/kg calculation for dosing. ABT-378/r appears to have a

good safety margin and there seems to be little reason to use the more complicated dosing by BSA recommendation. After careful examination of the PK data, Dr. Kim and the review team have proposed pediatric dosing recommendations using a mg/kg calculation that allow for dosing with or without NVP or efavirenz (another drug with which a significant interaction was identified in the adult clinical trials). This dosing recommendation is detailed in Sections 5 and 6.

4.2.3 Efficacy

The primary measure of efficacy in this study was the proportion of patients who reached and maintained an HIV RNA PCR value < 400 copies/ml at Week 24. There was no comparator group that did not receive ABT-378/r in this open label pediatric study but the 2 dose levels (230/57.5 and 300/75) were compared. Similarly, study subjects who were naïve to therapy were compared to those who had previously received other antiretroviral therapy. The sponsor performed both an on-study analysis and an intent-to-treat analysis of the primary and secondary endpoints but because the number of discontinued subjects was so small these proportions are virtually identical. Only one subject failed to complete 24 weeks of study and was prematurely discontinued because of the development of Burkitt's lymphoma. Independent analysis of the HIV RNA PCR data through 24 weeks of study confirmed the sponsor's conclusions regarding the efficacy of the treatment regimen in this pediatric population.

The analysis of the proportion of subjects with viral load < 400 copies/ml at Week 12 represents the last timepoint at which most of the study subjects remained on their original starting dose of ABT-378/r. After this timepoint subjects assigned to the lower dose were increased to the 300/75 mg dose for the remainder of the study. There was very little missing data that might have affected the results of the analysis. Only one subject (#434) had missing viral load data at Week 12 but both Week 8 and 16 measurements were < 400 copies/ml. As can be seen in Table 5, there is no significant difference in the proportion of study subjects achieving an undetectable viral load at Week 12 compared to Week 24.

Table 5: Proportion of Study Subjects with Undetectable Viral Load and Log Change in Viral Load at Week 24 (Intent-to-treat)

	Proportion < 400 copies/ml at Week 12	Proportion < 400 copies/ml at Week 24	Mean Log Change in HIV PCR from Baseline to Week 24
All Enrolled (N = 100)	74%	73%	-1.77
Group 1 (N = 49)	71%	73%	-1.90
Group 2 (N = 51)	78%	72%	-1.64
Naïve (N = 44)	82%	82%	-2.15
Experienced (N = 56)	70%	66%	-1.46
Age < 2 years (N = 14)	71%	71%	-1.68
Age ≥ 2 years (N = 86)	73%	73%	-1.78

None of the subgroup analyses revealed statistically significant differences between the 2 dose groups, between subjects younger or older than 2 years of age or between naïve and experienced subjects. A further analysis by the sponsor detected a significantly poorer response to ABT-378/r regimens in those experienced patients who had previously been treated with other protease inhibitors compared to treatment naïve subjects (58% compared to 82%). Of the 56 children enrolled in the study who had received prior antiretroviral therapy only 24 had received another protease inhibitor, but 21 of the 24 had received ritonavir.

The study report also describes the effect of the study regimen on CD4 and CD8 cell counts from the time of enrollment through Week 24. Subgroup analysis similar to that performed for viral load analysis was done on this data. It was expected that there would be a difference in the CD4 cell counts in children younger and older than 2 years of age due to the natural decline in these cell populations from infancy to age 5-6 years. The sponsor performed the CD4 cell count analysis using both log transformed data and the more commonly used arithmetic scale (absolute cell numbers). Confirmatory analysis was performed using only the absolute cell counts.

As can be seen in Table 6, mean CD4 cell counts increased over the 24 week period for the study population as a whole and for all subgroups evaluated. As expected, the relatively small group of participants who were < 2 years of age had higher mean CD4 counts at all timepoints than those ≥ 2 years. In one subgroup analysis this reviewer's results differed significantly from the sponsor's. The sponsor reported that the mean baseline CD4 for all patients was 838 cells/μl but also reports the mean baseline for Group 1 patients to be 1224 cells/μl and the mean baseline for Group 2 to be 1243 cells/μl. Mean changes in CD4 from baseline for

Groups 1 and 2 were reported as 433 cells/µl and 321 cells/µl respectively. In all other subgroups the reviewer's analysis was very similar to the sponsor's.

The difference is explained by a difference in method of calculating means. The sponsor analyzed CD4 cell count changes using a 2-way analysis of variance (ANOVA) without interaction with classification by dose and age group. Using this framework, least squares means were computed for baseline and change from baseline values. The sponsor suggests that this method using model-based, least squares means adjusts for imbalances in the CD4 counts of the younger and older age groups. It was listed in the study report as a secondary analysis.

Table 6: Mean Changes from Baseline to Week 24 for Absolute CD4 Cell Counts (cells/µl)

	CD4 Cell Counts at Baseline	CD4 Cell Counts at Week 24	Mean Change in CD4 from Baseline to Week 24
All Enrolled (N = 96*)	839	1171	332
Group 1 (N = 48*)	816	1203	386
Group 2 (N = 48*)	862	1139	278
Naïve (N = 44*)	920	1249	328
Experienced (N = 52*)	771	1105	335
Age < 2 years (N = 13*)	1765	2200	434
Age ≥ 2 years (N = 83*)	694	1010	316

* Calculations are based on number (N) of children with both baseline and Week 24 values. Including the 4 children with missing Week 24 values in the calculation of Baseline means and mean Change had no significant impact on the means.

Reviewer's comments:

Although this is an uncontrolled trial, these results are impressive when compared to previous, similarly-designed trials of other antiretroviral regimens in children. There appears to be no difference in antiviral efficacy for the two doses studied and no difference based on age at the time of study entry. The somewhat poorer results in the treatment experienced study subjects may partially reflect some of the errors in study protocol that resulted in 18 of 51 subjects in this group receiving potentially suboptimal regimens early in the study. In addition, prior use of ritonavir in the treatment experienced subjects may have had an impact on the study regimen efficacy, since there is some degree of cross-resistance between ritonavir and ABT-378. In general, these results are

similar to those seen in the larger, controlled, adult efficacy trials being reviewed contemporaneously.

The children enrolled in this study exhibited a wide range of viral loads and are representative of pediatric HIV patients at a relatively early stage of treatment. Thirty-nine percent of the study subjects had a viral load ≥ 10^5 copies/ml but only 2% had viral loads in excess of 10^6 copies/ml. Few of the patients had received multiple PI-containing regimens prior to entering the study. The mean baseline CD4 counts for patients enrolled was in the range considered to show evidence of no or mild immunosuppression (CDC classification for no immunosuppression: ≥ 1500 cells/ml for children < 1 year, ≥ 1000 cells/ml for children 1-5 years of age and ≥ 500 cells/ml for children ≥ 6 years). These characteristics define a population that is likely to give an optimal response to a new antiretroviral agent. This is not, however, the population most likely to receive the drug in the U.S. where the decline in perinatal transmission has left us with a population of HIV-infected children who are predominantly heavily pre-treated. Use of ABT-378/r in U.S. children may not yield results that are as impressive as those found in this clinical trial.

While the sponsor's method of calculating mean baseline CD4 counts and mean change from baseline CD4 may be statistically sound, it is an adjustment of the data which means little clinically and gives the impression that the study drug performed better than it did in this category. The adjustment made in their calculations gives added weight to the higher CD4 counts of the younger children who make up a minority of both the study population and the more general U.S. population of HIV-infected children. The CD4 count data reported in the drug label includes only the mean change from baseline for the subsets of children with and without prior antiretroviral treatment experience.

4.2.4 Safety

4.2.4.1 Overview of Adverse Events

All 100 patients who were enrolled in M98-940 were included in the sponsor's safety analysis. At the time of data analysis study subjects had received ABT-378/r for a range from 61 to 196 days. Only 1 patient received less than 84 days of study treatment (see Section 4.2.4.5) and only 4 received less than 168 days. The remaining 96 participants received from 168 to 196 days of the ABT-378/r regimen as of the time of this analysis.

At least one adverse event was reported during the study period by 99 of the 100 participants. The sponsor analyzed these events according to assigned COSTART terms and catagorized them according to intensity (mild, moderate, or severe) and causality (probably related to study drug, possibly related, probably not related and unrelated). A total of 494 adverse events were reported many of which were assigned more than one COSTART term. As expected, many of the events are those that are commonly seen in children, such as otitis media, fever and symptoms of gastroenteritis. Table 7 summarizes the sponsor's assessment of adverse events identified in ≥ 10% of the study subjects regardless of severity or causality.

Table 7: Adverse Events Reported during Study by 10% or More of Subjects Regardless of Severity or Causality

Body System/ COSTART Adverse Event	All Patients Enrolled (N = 100)	Group 1 230/57.5 mg (N = 49)	Group 2 300/75 mg (N = 51)
Body as a Whole			
Accidental injury	13 (13%)	7 (14.3%)	6 (11.8%)
Fever	24 (24%)	11 (22.4%)	13 (25.5%)
Infection	38 (38%)	18 (36.7%)	20 (39.2%)
Viral infection	10 (10%)	4 (8.2%)	6 (11.8%)
Digestive System			
Diarrhea	24 (24%)	9 (18.4%)	15 (29.4%)
Gastroenteritis	14 (14%)	7 (14.3%)	7 (13.7%)
Vomiting	27 (27%)	16 (32.7%)	11 (21.6%)
Respiratory System			
Cough increased	32 (32%)	17 (34.7%)	15 (29.4%)
Pharyngitis	46 (46%)	20 (20.8%)	26 (51.0%)
Rhinitis	25 (25%)	10 (10.4%)	15 (29.4%)
Skin and Appendages			
Eczema	16 (16%)	6 (12.2%)	10 (19.6%)
Rash	17 (17%)	9 (18.4%)	8 (15.7%)
Special Senses			
Conjunctivitis	16 (16%)	8 (16.3%)	8 (15.7%)
Otitis media	27 (27%)	13 (26.5%)	14 (27.5%)
Taste perversion	16 (16%)	8 (16.3%)	8 (15.7%)

Source: M98-940 Study Report, Tables 12.2.b and 12.2.d.

Gastrointestinal or digestive system (COSTART body system) events, diarrhea, gastroenteritis and vomiting, were among the most common events reported. At least 27% of patients experienced an episode of

vomiting during the first 24 weeks of the study. Three of these episodes were of at least moderate severity. Eleven patients reported 12 episodes of vomiting that were described in association with taking study medication; 7 of these within the first 2 days of initiating ABT-378/r. One of these episodes was graded as moderate in severity and all were thought to be possibly or probably related to study drug. Diarrhea, either alone or as part of a gastroenteritis syndrome, was also frequently reported. Twenty-five children (25%) reported 35 episodes of diarrhea (one designated as bloody diarrhea) during the study period and an additional 14 children were reported to have gastroenteritis. Twenty of the episodes of diarrhea were probably, possibly or probably not attributed to study drug while 13 of the gastroenteritis events were considered possibly related or probably not related.

Respiratory system events were also frequently reported in this population of children. It should be noted that in this system, the intrinsic difficulties of the COSTART classification might give an inaccurate assessment of the events. While 46 children are reported to have had "pharyngitis," the clinical description of 32 of these children was that of upper respiratory tract infection, a term that pediatricians frequently use synonymously with the common cold. Some of these events may have been coded as "viral infection" and reported in a different category. These are extremely common illnesses in children and it would be difficult to attribute any increased incidence to use of ABT-378/r. Few of these events were felt to be possibly or probably related to study drug.

Taste perversion was reported as an adverse event in 16 subjects. In all cases this reflected the poor palatability of ABT-378/r and was described as complaints about the medication's bad or bitter taste. Twelve of the 16 subjects reporting this as an adverse event were from a single site. Another 2 subjects, coded as "personality disorder," were described as refusing to take or spitting out study medications. These events were equally divided between the 2 dose groups and all were considered probably related to study drug.

Of the adverse events described, 10 events reported by 6 patients were of at least moderate severity and thought to be possibly or probably related to ABT-378/r. These events are summarized in Table 8. Two of the events coded as probably related to ABT-378/r involved rash and fever.

Table 8: Adverse Events Considered to be Possibly or Probably Related to ABT-378/r and at least Moderate in Severity

Subject Number	Dose Level	Event Description (COSTART term if different)	Severity of Event	Relationship to Study Drug (Investigator)
203	300	Constipation	Moderate	Possible
313*	300	Viral infection	Moderate	Possible
		Dry skin	Moderate	Possible
		Rash	Moderate	Possible
		Hepatomegaly	Moderate	Possible
331	230	Vomiting	Moderate	Probable
405	300	Dislikes taste of ABT-378/r (taste perversion)	Moderate	Probable
428	300	Hypersensitivity reaction with fever, rash, jaundice (allergic reaction)	Moderate	Probable
447*	230	Fever	Moderate	Probable
		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.

4.2.4.2 HIV-related Events

Eight children experienced HIV-related events during the first 24 weeks of the study. One of these events, the HIV-related Burkitt's lymphoma, resulted in death. Other than the lymphoma, all HIV-related events were rated as mild except for one episode of pneumonia rated as moderate in severity. Other children with HIV-related events included: 2 children with oral candidiasis (thrush), and 1 each with other candidiasis (candida dermatitis), chronic ulcers, herpes simplex (herpes labialis), herpes zoster, and recurrent pneumonia.

4.2.4.3 Serious Adverse Events

The sponsor reported serious adverse events occurring in 16 patients. Seventeen subjects, 4 of whom experienced ≥ 2 serious events, were identified during the review. Subject #431 was reported to have had multiple hospitalizations related to Burkitt's lymphoma and is described in detail in Section 4.2.4.5. Subject #432 had apparently elective hamstring release surgery that was reported as a study SAE. All SAE's including the 2 mentioned above are summarized in Table 9 along with their severity rating and the investigator's assessment of relationship to study drug. As

can be seen, most of the events were considered not related to the study drug. In the case of Subject #431, prior to the diagnosis of lymphoma the investigator considered one of his events (hypersensitivity reaction) probably related to study drug. In retrospect the sponsor felt that these events were all related to lymphoma and consequently considered them not related to study drug.

Table 9: Serious Adverse Events According to Dose Level

Subject Number	Dose Level	Event Description (COSTART term if different)	Severity of Event	Relationship to Study Drug (Investigator)
102*	−300/75	Pneumonia, right basal Pneumonia, right	Mild Moderate	Not related Not related
106	230/57.5	Dacryocystitis (infection bacterial)	Mild	Not related
107	300/75	Bilateral pneumonia Chronic otitis media	Severe Severe	Not related Not related
201	230/57.5	Wheezing (asthma)	Mild	Not related
302	300/75	Pneumococcal sepsis with reactive arthritis (sepsis)	Severe	Not related
308	230/57.5	Dysentery (bloody diarrhea)	Severe	Probably not
324	230/57.5	Gastroenteritis	Severe	Probably not
402	230/57.5	Viral syndrome (infection viral)	Severe	Probably not
410	230/57.5	Infected burns (infection)	Moderate	Not related
422	230/57.5	Otitis media	Moderate	Not related
428	300/75	Varicella (infection viral)	Moderate	Not related
431*	230/57.5	Hypersensitivity reation Cellulitis left leg Burkitt's lymphoma Echthyma gangrenosum	Moderate Mild Severe Severe	Probable Not related Not related Not related
432	300/75	Spastic diplegia needing hamstring release surgery (reaction unevaluable)	Mild	Not related
434	300/75	Otitis media with perforation Impetigo (infection bacterial)	Moderate Moderate	Not related Probably not
438*	230/57.5	Viral syndrome Viral syndrome Serous otitis media	Moderate Mild Mild	Probably not Probably not Probably not
442	300/75	Fever Cough (cough increased) Rhinitis	Moderate Moderate Moderate	Probably not Probably not Probably not
443	230/57.5	Bullous impetigo (infection)	Moderate	Not related

*More than one event requiring hospitalization

These events are representative of illnesses that occur in the HIV-infected pediatric population and might be seen with any therapeutic regimen. No identifiable pattern could be determined.

4.2.4.5 Interruptions of Therapy Related to Adverse Events

During the 24 week study period there were 6 subjects who had study regimen interrupted due to adverse events. One study subject developed asymptomatic pancreatitis. Another had treatment interrupted secondary to vomiting the medications. Four patients developed rashes, all of whom also had fever and 2 of whom developed abnormal liver function tests during the same episode. One of these events was coded as a "hypersensitivity reaction or allergic reaction" accompanied by hepatitis and was attributed to NVP, while another episode of rash with fever and conjunctivitis was "presumed caused by NVP" and a third episode of rash and fever (also in a patient receiving NVP) was described as "drug induced". The fourth patient requiring treatment interruption secondary to rash was a treatment naïve patient diagnosed with a viral illness thought to be EBV infection. Another study participant had study drugs interrupted and later prematurely discontinued due to a series of adverse events finally diagnosed as Burkitt's lymphoma. For details of this patient's course see Section 4.2.4.5 below.

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 ABT-378/r, 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 ABT-378/r, 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. This child subsequently had an episode of symptomatic pancreatitis after the initial 24 weeks of study, reported in the last safety update. 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 ABT-378/r but also possibly related to either d4T or abacavir.

Reviewer's comments:
The pattern of adverse events reported in M98-940 is very similar to that reported in the adult clinical trials. Gastrointestinal side effects should be anticipated as the major toxicity, as well as a small proportion of patients who may develop rashes. Many of the rash events reported in this study were attributed to other antiretroviral agents, particularly NVP. All cases of moderately severe rash considered probably ABT-378/r related occurred in subjects who were receiving NVP.

More noticeable in the pediatric studies are complaints related to the palatability of the formulation (most often coded as taste perversion). This is not surprising since this compound requires formulation with excipients such as alcohol and castor oil and the track record of ritonavir solution's poor palatability is well known. In spite of the unpalatable formulation, no patients withdrew from the study for this reason.

4.2.4.6 Deaths

One patient died during the 24 week study period. Subject #431 was prematurely discontinued from study on Day 93 after being diagnosed with Burkitt's lymphoma. A summary of this subject's clinical course is included below.

The subject was a 6 year old boy with a history of prior antiretroviral therapy who was randomized to receive the 230/57.5 mg dose of ABT-378/r. At the time of the adverse events he was receiving ABT-378/r at 300/75 mg, along with NVP, stavudine, didanosine and abacavir. Prior to study discontinuation he had been hospitalized several times for illnesses that were initially diagnosed as hypersensitivity reaction, eye swelling and cellulitis, leg cellulitis, and finally vomiting, dehydration and bone pain. He was treated with a variety of medications including antibiotics, diuretics and systemic and inhaled steroids. Study drug was interrupted for approximately 4 weeks during the first hospitalization and resumed prior to his final hospitalization. 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. In retrospect, all prior diagnoses were thought to be related to the lymphoma. The subject received antineoplastic therapy, study treatment and supportive care. Complications of his course included GI bleeding and thromocytopenia, fever with neutropenia, oral herpes and candidiasis. All study drugs were permanently discontinued on 11/30/99 and he died a few weeks later after developing echthyma gangenosum and sepsis. His

hospitalizations and death were not considered related to study medications.

4.2.4.7 Laboratory Abnormalities

The sponsor analyzed changes in mean laboratory values from baseline to each study visit and also looked for the incidence of certain pre-defined extreme values and laboratory abnormalities that were reported as adverse events. "Consistently statistically significant mean changes from baseline" were defined for serum chemistry and hematology values as changes in the same direction in at least 50% of evaluations and having p-values of < 0.05. These were the values reported by the sponsor. Most of the identified changes from baseline were small and, therefore, clinically insignificant. Monitoring laboratory assays were not performed at a central site and assay reference ranges differed according to site. These analyses include a small number of children who had baseline clinical laboratory values that were higher than normal (refer to Section 4.1.5, Protocol Deviations).

Clinical Chemistry Monitoring

The sponsor reported consistently statistically significant mean changes from baseline for several clinical chemistry variables at different study timepoints. These changes at study Weeks 12 and 24 are summarized in Table 10. Some of the variables were also significantly different from baseline at other timepoints; the Weeks 12 and 24 values are shown as examples of the magnitude of change.

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Table 10: Consistently Significant Mean Changes from Baseline for Chemistry Variables for all Subjects Enrolled

Chemistry Variable	Baseline Mean	Mean Change from Baseline	P-value
Sodium (mEq/L)	136.50		
Week 12		1.99	<0.001
Week 24		2.64	<0.001
Chloride (mEq/L)	104.00		
Week 12		0.97	0.01
Week 24		1.28	0.002
Calcium (mg/dL)*	9.30		
Week 12–		0.13	0.018
Inorganic Phosphorus (mg/dL)	5.35		
Week 12		-0.44	<0.001
Week 24		-0.24	0.002
Total Protein (g/dL)	8.63		
Week 12		-0.53	<0.001
Week 24		-0.49	<0.001
Albumin (g/dL)	3.78		
Week 12		0.08	0.03
Week 24		0.13	<0.001
Alkaline Phosphatase (IU/L)	202.05		
Week 12		36.78	<0.001
Week 24		44.63	<0.001
LDH (IU/L)**	285.91		
Week 24		-26.54	<0.001
Creatinine (mg/dL)**	0.33		
Week 24		0.02	0.022
Cholesterol (mg/dL)	134.50		
Week 12		26.76	<0.001
Week 24		33.69	<0.001
Triglycerides (mg/dL)	112.66		
Week 12		25.54	0.006
Week 24		25.31	<0.001
Amylase (IU/L)**	89.36		
Week 24		-12.37	0.004

*Week 24 mean change not significant.
**Week 12 mean change not significant.
Source: M98-940, Study Report, page 154.

The only changes from baseline that might be of clinical concern are those involving cholesterol and triglycerides. The increases of 33.69 and 25.31 respectively at Week 24 may have clinical impact. The sponsor suggests that these changes may be related to the pediatric clinical trial practice of drawing monitoring laboratory studies without regard to fasting. The sponsor also identifies a small but significant difference in mean change from baseline observed for at least 50% of the timepoints for total bilirubin, SGPT, SGOT, total protein and amylase when subjects were stratified according to treatment experience. These changes primarily reflected small decreases in the mean laboratory values and were clinically irrelevant.

- Another way of reviewing the data is to evaluate the number of children who had serum chemistry values at some pre-defined extreme level. The sponsor defined these very high and very low values for all chemistry variables. The numbers of children developing these extreme laboratory values are summarized in Table 11 according to dose level. There did not appear to be any differences in extreme laboratory values at the 300/75 dose compared to the 230/57.5 dose.

Table 11: Numbers of Subjects with Extreme Clinical Chemistry Values by Dose Group

Chemistry Variables Very High	Indicator Criteria	Dose Group 1 (N = 49)	Dose Group 2 (N = 51)
Uric Acid	Age < 2y: > 1.1 mg/dL Age ≥ 2y: > 1.6 mg/dL	1	0
Sodium	> 149 mEq/L	0	1
Calcium	> 11.9 mg/dL	1	0
Total Bilirubin	> 2.9 x ULN	2	1
SGOT	≥ 10 x ULN	0	1
SGPT	≥ 10 x ULN	1	1
Cholesterol	> 300 mg/dL	1	1
Triglycerides	> 750 mg/dL	1	0
Amylase	>2.5 x ULN	1	3
Chemistry Variables Very Low			
Sodium	< 130 mEq/L	1	2
Potassium	< 2.5 mEq/L	1	0

ULN = upper limit of normal value
Source: M98-940 Study Report, page 160.

For some laboratory variables, the sponsor's definition of very high or very low values appears too liberal. SGOT and SGPT values of ≥ 10 x ULN represent a Grade 3 toxicity in the consensus pediatric rating scales, indicating moderately severe liver dysfunction or injury. If a more conservative cut-off of ≥ 5 x ULN for the liver transaminases is used, approximately twice as many subjects would be identified with extreme values. The Grade 3 toxicity criteria is, however, used for identifying the extreme values for most clinical chemistry variables.

Reviewer's comments:
Some of the changes in serum chemistries may reflect the normal age-related differences in physiologic variables, such as higher alkaline phosphatase values in growing children. Others may reflect the effects of the study regimen, such as changes in cholesterol and triglycerides. In most cases the magnitude of the changes, even though statistically significant and consistent within the study population, is so small that the clinical significance is negligible.

Other protease inhibitors, especially ritonavir, have been shown to predispose to liver toxicity, pancreatitis and increased serum lipids in adult HIV-infected patients. These potential toxicities are identified in this pediatric trial but at relatively low frequencies. In the population studied, mean levels of SGOT and SGPT decreased over the first 24 weeks. A small number of children had levels that were in the extreme range, though half of the population was also receiving NVP, another agent known to be associated with liver toxicity. In children, the correct identification of asymptomatic or chemical pancreatitis is sometimes obscured by the finding of increased salivary amylase. Similarly, the identification of serum lipid abnormalities may be overlooked as care providers acknowledge that children rarely have levels measured in the fasting state. In this trial a small number of children were identified with elevated total amylase (supported by elevated pancreatic amylase in some cases) and one was ultimately removed from study because of symptomatic pancreatitis and persistent hyperamylasemia. Only one child had triglycerides > 750 mg/dL (3 with > 500 mg/dL) and 2 had cholesterol > 300 mg/dL. One of these children entered the study with markedly elevated cholesterol and triglyceride levels.

Hematology Monitoring

Clinical hematology laboratory values were evaluated in the same way as the chemistry values. There were several hematology variables that exhibited mean changes from baseline in the study population as a whole. These changes are summarized in Table 12; again study values at Weeks 12 and 24 are shown as representative of the magnitude of change. Table 13 lists the numbers of subjects who developed extreme hematology

laboratory values during the first 24 weeks of study stratified by dose group.

Table 12: Consistently Significant Mean Changes from Baseline for Hematology Variables for all Subjects Enrolled

Hematology Variable	Baseline Mean	Mean Change from Baseline	P-value
Lymphocytes (x 10^9/L)	3.54		
Week 12		0.70	<0.001
Week 24		0.57	<0.001
Monocytes (x 10^9/L)	0.41		
Week 12–		0.10	0.004
Neutrophils (x 10^9/L)	2.89		
Week 12		0.75	0.003
Week 24		0.36	0.041
RBC (x 10^{12}/L)	4.22		
Week 12		-0.11	0.009
Week 24		-0.22	<0.001
MCV (fl)	84.76		
Week 24		4.63	<0.001
MCHC (g/dL)	32.47		
Week 12		0.58	0.003
Week 24		1.01	<0.001
WBC (x 10^9/L)	7.18		
Week 12		1.52	<0.001
Week 24		0.98	<0.001
Prothrombin Time (sec)	12.59		
Week 24		-0.36	<0.001

Source: M98-940 Study Report, Page 146.

Table 13: Numbers of Subjects with Extreme Hematology Values (Very Low) by Dose Group

Hematology Variables	Indicator Criteria	Dose Group 1 (N = 49)	Dose Group 2 (N = 51)
Hemoglobin	< 7 g/dL	1	0
Platelet count	< 50 x 10^9/L	2	2
Neutrophils	< 0.4 x 10^9/L	1	1

Source: M98-940 Study Report, Page 149.

As can be seen from the tables, most of these changes in the population as a whole reflect small increases in each reported variable. The observed

decreases in RBC values over time were not accompanied by significant decreases in either hemoglobin or hematocrit. As with the changes in chemistry values, most of these changes are clinically insignificant. Of interest, 3 of the 4 subjects with very low platelet counts were children who had not been previously treated for HIV infection.

Reviewer's comments:
Although this is a relatively small study, the changes in hematology variables identified in this study population do not raise any concerns for serious toxicity. As the drug is used for longer periods, both in the clinical trial and later in broader usage, care providers will need to be observant regarding the potential for decreases in RBC measurements. The finding of 4 children with extreme thrombocytopenia is worrisome but 3 of these children had a single, recorded platelet count at Week 3 of $<50 \times 10^9/L$ 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 is subject #431 who developed Burkitt's lymphoma. There is no evidence to suggest that the drug exhibits significant bone marrow toxicity at this time.

5.0 Conclusions

Despite the advances in highly active antiretroviral therapy of the last few years, there remains a critical need for pediatric age-appropriate formulations of these agents. At present only 3 of the 5 available protease inhibitors have a formulation for younger children who cannot swallow tablets or capsules. Of these 3, ritonavir oral solution is approved for use in children > 2 years, nelfinavir oral powder is approved for use in children > 2 years and amprenavir oral solution is approved for use in children > 4 years. Obviously, pediatricians and other health care providers use these and other antiretroviral medications off-label in infants and younger children. A critical need exists for information regarding the use of new agents in all children but particularly in those < 2 years.

The NDA for ABT-378/r includes data from a single pediatric study (M98-940) on the safety, pharmacokinetics and antiviral activity of 2 doses of the drug in a combination antiretroviral regimen. This multi-national, open-label study enrolled 100 children from 6 months to 12 years of age with 44% of participants naïve to antiretroviral therapy at the time of study entry and 14% < 2 years of age. Safety monitoring and measurements of HIV RNA PCR and lymphocyte subset analysis were performed monthly. The sponsor obtained adequate sampling to determine ABT-378/r's PK profile in 53 children, 12 of whom were < 2 years. These data are sufficient to make preliminary conclusions about the drug's optimal dosing and it's safety and efficacy over 24 weeks in a population of relatively well HIV-infected children.

Evidence of substantial antiviral activity over the 24 week study period was provided by analysis of the proportion of children whose viral load decreased during the study to below 400 copies/ml, the lower limit of detection. Overall, 73% of the study subjects reached and maintained an undetectable viral load at 24 weeks. This proportion was higher for the group of children who were naïve to therapy at the time of study entry (82%) compared to those who had previously received other antiretroviral therapy (66%). This was accomplished through a mean change in log HIV RNA PCR of -1.77 over the 24 week period in the study population. As might be expected, treatment naïve subjects exhibited a greater mean change in log HIV RNA PCR (-2.15) than treatment experienced subjects (-1.46). These treatment effects were similar for children < 2 years of age as well as those > 2 years. There was no apparent dose effect when the 2 dose levels were compared, although patients were escalated from the lower dose level to the higher level at 12-16 weeks and this could mask potential differences in efficacy.

These changes in viral load were accompanied by corresponding increases in CD4 cell counts. The study population as a whole and all subgroups analyzed had significant improvements in CD4 cell counts with the mean CD4 count increasing by 332 cells over the 24 week period for the whole population. As would be expected based on the normal age-related decline in CD4 cells, the subgroup of subjects < 2 years had the highest baseline CD4 counts (1765 cells) and exhibited the greatest increase over time (434 cells). Even without the effect of the younger children "weighting" the mean, the study subjects > 2 years of age had a very good CD4 response with a mean increase of 316 cells.

This study was not controlled or blinded to dose level so it is difficult to determine precisely the effect of ABT-378/r as distinct from the other agents in the antiretroviral regimen. However, these results would argue that ABT-378/r is an effective component of a highly active regimen. None of the minor protocol deviations identified during the review detract from the efficacy of the regimens studied in either treatment naïve or experienced children. The dosing errors that occurred at 2 sites may have led to an underestimation of the potency of the treatment regimen but there was no obvious difference in effect in this patient group.

The safety profile of ABT-378/r characterized in this study is very similar to that seen in adult HIV-infected subjects. Gastrointestinal complaints including vomiting and diarrhea were relatively common, occurring in 27% and 24% respectively of the pediatric study population. Many of the episodes of vomiting were reported to be associated with taking study medications. Respiratory symptoms such as increased cough, pharyngitis and rhinitis were also commonly reported. While a majority of the reported GI complaints were considered probably, possibly or probably not related to study drug, very few of the respiratory complaints were attributed to ABT-378/r. This probably reflects the frequency of upper respiratory tract symptoms in children and the difficulty of attributing causality to the drug. Relatively few of the adverse events were graded as severe in intensity and none of the serious adverse events reported with this submission could be clearly attributed to use of study drug. The single case of symptomatic pancreatitis that

occurred after the first 24 weeks of study was probably related to the study regimen but was attributed in part to the other components of the regimen.

The types and frequencies of laboratory abnormalities are also similar to those seen in adult patients with a few exceptions. In the pediatric study most of the statistically significant changes in laboratory values were small and clinically insignificant. The reported increases in cholesterol and triglycerides are difficult to interpret since most of the monitoring laboratory studies were performed in the non-fasting state. It is likely that this reflects the capacity of the protease inhibitors, in this case ABT-378/r, to increase these values. Episodes of clinically significant liver dysfunction, pancreatitis and hyperlipidemia were uncommon but were reported and in some cases led to interruption of ABT-378/r. No convincing evidence of bone marrow toxicity was identified during the study but minor changes in total RBC's were seen and 4 cases of thrombocytopenia were reported. The significance of the reported thrombocytopenia is questionable as 3 of the 4 cases were isolated values that resolved without intervention over a short period. As the drug is used in a larger and more varied population of HIV-infected children the real frequency of these adverse events and laboratory abnormalities will be better understood.

While no clinical events have been associated to date with the large amount of ethanol contained in ABT-378/r oral solution, this does cause some concern. The American Academy of Pediatrics has urged pharmaceutical manufacturers to reduce the amount of ethanol in pediatric formulations and, if possible, eliminate it completely from both OTC and prescription drugs. The difficulty of getting the protease inhibitors into solution has led to the use of large quantities of excipients such as ethanol, propylene glycol and castor oil that have potential undesirable effects. In this case, the theoretical risks of chronic ingestion of small amounts of ethanol (to a parent the equivalent of 1-2 teaspoons of vodka, scotch or other liquor every day) may be offset by the potential benefits of a highly active antiretroviral drug. Parents and pediatricians, however, should be warned of the risks of drug interactions (children are unlikely to take disulfiram but might receive metronidazole) and of accidental overdose of ethanol. The accepted potentially lethal dose of ethanol in children is 3 g/kg. Accidental ingestion of a full 160-ml bottle of ABT-378/r by a toddler or small child could reach this level.

Given the acceptable safety profile and good antiretroviral activity of ABT-378/r, there appears to be a wide therapeutic index. In this study 2 doses were studied in children: 230/57.5 mg, a dose equivalent to that used in the adult Phase III trials, and 300/75 mg, a dose calculated to account for children's more rapid clearance of many drugs (including ritonavir). Both dose levels were initially thought to give ABT-378 exposure similar to that seen in the adult clinical trials but the higher dose was selected for further study because it exhibited a PK profile more similar to a pre-defined target. Further analysis of the PK data revealed a significant interaction with nevirapine, one of the other components of the regimen used in treatment experienced children. This interaction produces lower ABT-378 exposure in children receiving concomitant nevirapine than

those not receiving nevirapine. A similar interaction was found in adults using efavirenz concomitantly with ABT-378/r.

After careful review of the PK and safety data it was decided that it was both possible and desirable to convert the dosing recommendations to a mg/kg dose. Eliminating the mg/m^2 BSA calculation reduces the potential for errors in calculating doses. Since a relatively small proportion of children who might receive the drug are likely to also receive either nevirapine or efavirenz it was also considered appropriate to give separate dosing recommendations for children taking these drugs. This is similar to the approach suggested for adult dosing guidelines. We have recommended that the dosage of ABT-378/r oral solution should be 12 mg/kg (of the lopinavir component) twice daily for children < 15 kg and 10 mg/kg twice daily for children 15 – 40 kg, taken with food, up to a maximum dose of 400/100 mg (5.0 ml) twice daily. If given in a regimen containing either nevirapine or efavirenz in treatment experienced children who may have some reason for decreased susceptibility to ABT-378/r (ie, patients who have received other PIs), the dose of ABT-378/r should be increased to 13 mg/kg for children < 15 kg and 11 mg/kg twice daily for children 15 – 50 kg. Children older than 12 should be dosed according to adult recommendations.

In summary, the sponsor has presented data from a well-designed pediatric clinical trial supporting the approval of ABT-378/r for use in treating HIV infection in children 6 months to 12 years of age. Review of the PK, safety and tolerability, and preliminary efficacy data from this trial reveals no major concerns and confirms the sponsor's claim that the drug may be a valuable addition to the anti-HIV armamentarium for children. Recommendations for dosing by body weight rather than BSA and for additional warnings concerning the potential for toxic acute ingestion of ethanol have been discussed with the sponsor. Additional studies evaluating drug interactions with other PIs and other commonly used drugs and evaluating the use of Kaletra in more heavily pre-treated patients have been agreed to in the Phase 4 commitments associated with the capsule formulation (NDA 21-226).

6.0 Labeling

The sponsor proposes a single package insert for both the capsule and oral solution formulations of ABT-378/r. Pediatric PK information is described in the Pharmacokinetics, Special Populations Section. The Indications and Usage Section contains a Pediatric Use subsection describing the design and results of M98-940. Finally, the Dosage and Administration Section contains recommendations for pediatric dosing and a table giving pediatric dosing guidelines. The review team has suggested the following modifications in the sections of the label pertaining to the oral solution and pediatric use.

In the **DESCRIPTION** section that contains chemistry information the sponsor has stated that:

> KALETRA oral solution contains 42.4% alcohol (v/v).

We propose that this statement be printed in bold font.

In the **Pharmacokinetics, Special Populations** section the sponsor has proposed:

The FDA has proposed that the pharmacokinetic data from all 53 children studied be included in the label with special emphasis on the subsets most pertinent to the recommended doses. The following wording has been proposed:

> Pediatric Patients: The pharmacokinetics of KALETRA 300/75 mg/m^2 BID and 230/57.5 mg/m^2 BID have been studied in a total of 53 pediatric patients, ranging in age from 6 months to 12 years. The 230/57.5 mg/m^2 BID regimen without nevirapine and the 300/75 mg/m^2 BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).
>
> The lopinavir mean steady-state AUC, C_{max} and C_{min} were 72.6±31.1 μg•h/mL, 8.2±2.9 and 3.4±2.1 μg/mL respectively after KALETRA 230/57.5 mg/m^2 BID without nevirapine (n=12) and were 85.8±36.9 μg•h/mL, 10.0±3.3 and 3.6±3.5 μg/mL, respectively after 300/75 mg/m^2 BID with nevirapine (n=12). The nevirapine regimen was 7 mg/kg BID (3 months to 8 years) or 4 mg/kg BID (>8 years).

In the OVERDOSAGE section we propose that the sponsor add the following:

KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

In the **DOSAGE AND ADMINISTRATION** the sponsor has suggested the following text and pediatric dosing guidelines in table format:

Pediatric Patients
The recommended dosage of KALETRA oral solution is 300/75 mg/m2 twice daily taken with food, up to a maximum dose of 400/100 mg (5.0 mL) twice daily.

Pediatric Dosing Guidelines	
Body Surface Area (m2)	**Twice Daily Dose (300/75 mg/m2)**
0.25	0.9 mL (75/18.75 mg)
0.50	1.9 mL (150/37.5 mg)
0.75	2.8 mL (225/56.25 mg)
1.00	3.8 mL (300/75 mg)
1.25	4.7 mL (375/93.75 mg)
1.33	5 mL (400/100 mg)

In the **DOSAGE AND ADMINISTRATION: Pediatric Patients** we propose:

In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to < 15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children > 40 kg (5.0 ml or 3 capsules) twice daily. The following table contains dosing guidelines for KALETRA oral solution based on body weight.

Weight (kg)	**Dose (mg/kg)***	**Volume of oral solution (80mg lopinavir/20mg ritonavir per mL)**
Without nevirapine or efaverinz		
7 to < 15 kg	12mg/kg	
7 to 10 kg		1.25 mL
>10 to 15 kg		1.75 mL
15 to < 40 kg	10 mg/kg	
>15 to 20 kg		2.25 mL
>20 to 25 kg		2.5 mL
>25 to 30 kg		3.0 mL
>30 to 40 kg		3.5 mL
>40 kg	adult dose	5 mL (or 3 capsules)

*Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children > 12 years of age.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to < 15 kg and 11/2.75 mg/kg for those 15 to 50 kg (approximately equivalent to 300/75 mg/m^2) twice daily should be considered when used in combination with efavirenz or nevirapine in treatment experienced children 6 months to 12 years or age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Weight (kg)	**Dose (mg/kg)***	**Volume of oral solution (80mg lopinavir/20mg ritonavir per mL)**
With nevirapine or efaverinz		
7 to < 15 kg	13mg/kg	
7 to 10 kg		1.5 mL
>10 to 15 kg		2.0 mL
15 to < 50 kg	11 mg/kg	
>15 to 20 kg		2.5 mL
>20 to 25 kg		3.25 mL
>25 to 30 kg		4.0 mL
>30 to 40 kg		4.5 mL
>40 to 50 kg		5.0 mL (or 3 capsules)
> 50 kg	adult dose	6.5 mL (or 4 capsules)

*Dosing based on the lopinavir component of lopinavir/ritonavir solution (80mg/20mg per mL)
Note: Use adult dosage recommendations for children > 12 years of age

7.0 Regulatory Recommendations

This reviewer suggests approval of KALETRA oral solution (lopinavir/ritonavir, ABT-378/r) for the treatment of HIV infection in children 6 months to 12 years of age, pending agreement to above recommended changes in label and agreement to Phase 4 commitments associated with NDA 21-226. We have deferred studies in infants < 6 months of age and have issued a Written Request for studies in this population to be completed by 2003.

/S/

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DAVDP/ODE IV/CDER/FDA

Concurrence:
HFD-530/Div Dir/Jolson /S/ 10/2/00
HFD-530/TL/Murray 9/27/00

Cc:
Orig. IND
HFD-530/Division File
HFD-530/CSO/Holloman
HFD-530/MO/Lewis
HFD-530/MO/Struble
HFD-530/TL/Murray