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**Application Number** 20-977 ✓ 20-978

**MEDICAL REVIEW(S)**

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NDA 20-977

NDA 20-977  
NDA 20-978

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OCT 12 1999

**Medical Officer Review**  
**NDA 20-977**  
**NDA 20-978**

**Date of submission:** June 24, 1998  
**Date received:** June 24, 1998  
**Date assigned:** June 24, 1998  
**MOR completed:** December 15, 1998  
**Revisions completed:** October 8, 1999

**Applicant:** Glaxo Wellcome Inc.  
Five Moore Drive  
Research Triangle Park, NC 27709

**Drug Class:** HIV-1 reverse transcriptase inhibitor, nucleoside analogue

**Drug Name:** (1S,4R)-4-(2-amino-6(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-methanol succinate (1592U89)

**Generic:** abacavir sulfate

**Trade:** Ziagen™

**Dosage Form:** 300 mg tablets (NDA 20-977)  
20 mg/mL oral solution (NDA 20-978)

**Proposed Indication:** Treatment of HIV infection

**Proposed Dosage:** 300 mg BID (adults)  
8 mg/kg BID (pediatrics)

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#### **A. Resume**

Two NDA's for abacavir sulfate were submitted by Glaxo Wellcome Inc. for consideration under 21 CFR 314 Subpart H (accelerated approval regulations). NDA 20-977 was submitted in support of approval of the 300 mg tablet, and contains all clinical and non-clinical data to support both the tablet and the oral solution with the exception of the chemistry, manufacturing, and control data submitted in support of the oral solution, which is submitted in NDA 20-978. This clinical review is therefore confined to data submitted to NDA 20-977, and these data will be considered supportive of both NDA's.

As permitted under the accelerated approval regulations, surrogate endpoint data (viral load and CD4 cell count changes) from adequate and well-controlled studies (in adults and children) (CNAB 3003, CNA 3006, and CNAB 3005) were submitted in support of the efficacy of abacavir sulfate to treat HIV infection. These data provide evidence that treatment with abacavir in combination with other antiretroviral agents lowers viral load and increases CD4 cells counts through 16-24 weeks of therapy in treatment-naive HIV-infected patients. Only limited benefit to nucleoside analogue-experienced patients was demonstrated. Data from these trials, and from phase 1 and 2 studies support the proposed marketing dose of 300 mg BID for adults and 8 mg/kg for pediatrics.

The most concerning adverse event associated with abacavir treatment is hypersensitivity reaction to abacavir, reported in at least 5% of subjects enrolled in clinical trials of abacavir. If unrecognized, severe, or upon re-challenge, hypersensitivity reactions have resulted in deaths. Dissemination of information about this reaction will include a boxed warning, descriptions in the warnings, precautions, and adverse events sections in the label, and provision to patients of a Medication Guide and wallet warning card with each new prescription of abacavir. Commitment by the applicant to comprehensive study of this serious adverse event is outlined in the phase 4 commitments.

Other adverse events associated with short-term abacavir therapy in the phase 3 clinical trials include nausea and vomiting, headache, and malaise or fatigue. Laboratory adverse events associated with abacavir therapy are generally similar to those associated with other nucleoside analogue agents. Mild elevations of blood glucose were associated with abacavir therapy in three controlled trials. Triglyceride elevations (all grades) were detected more frequently in subjects receiving abacavir in study CNAB 3003. Conclusions about the long-term safety profile of abacavir cannot be made at this time.

The data in this application support the conclusion that abacavir sulfate has an effect on surrogate endpoints that is reasonably likely to be associated with clinical benefit. At least one study, CNAB 3005, likely to support the clinical benefit of abacavir as evidenced by long-term viral load suppression (minimum of 48 weeks) for treatment of HIV infection with abacavir is underway. The applicant has committed to initiating a second study to confirm clinical benefit.

## B. Background

### B. 1 Regulatory History

The IND for abacavir was submitted on June 1, 1994, and the initial phase I single dose pharmacokinetic study in adults was allowed to proceed on June 24, 1994. Phase 2 studies were initiated in February 1995, and a phase 1 study in pediatrics was initiated in March 1995.

The end-of-phase 2 meeting was held in January 1997, and the phase 3 development plan was reviewed at a closed session of the Antiviral Advisory Committee in February 1997. Phase 3 studies were initiated in March 1997. The pre-NDA meeting was held in February 1998. This NDA was presented at an open session of the Antiviral Advisory Committee on November 2, 1998. The committee voted for approval of abacavir under the accelerated approval regulations; seven votes were in support of approval and two votes were against approval. The committee recommended that the applicant commit to the widest possible dissemination of information about hypersensitivity reactions.

Abacavir is not approved in any country for commercial use.

### B. 2 Phase 2 studies

#### B. 2.1 CNA 2001

CNA 2001 was a 12 week dose-finding and activity study in which several doses of abacavir were evaluated in treatment-naive patients as monotherapy and in combination with zidovudine. Subjects entered with median baseline HIV RNA levels of 4.8 log<sub>10</sub> copies/mL and median baseline CD4 counts of 370 cells/mm<sup>3</sup>, and were predominantly Class A in the CDC Classification. Treatment switches were not allowed. Table 1 shows virologic activity at four and 12 weeks.

Table 1: Median HIV RNA log<sub>10</sub> change from baseline in Study CNA 2001

	200 mg TID n=16	400 mg TID n=19	300 mg BID n=20	600 mg TID n=17
Baseline HIV RNA	5.11	4.56	4.5	4.94
Week 4	-1.65	-1.34	-1.11	-1.77
Week 12				
ABC/ZDV	-1.89 (n=7)	-1.90 (n=9)	-1.81 (n=10)	-2.01 (n=10)
ABC/PBO	-2.24 (n=8)	-1.18(n=10)	-1.02 (n=10)	-1.34 (n=7)

Median CD4 increases at four weeks and 12 weeks were +63 cells/mm<sup>3</sup>, and +90 cells/mm<sup>3</sup> respectively. The results of this study were not sufficient to identify a dose-response based on differences in either viral RNA or CD4 cell counts, so a second study (CNAB 2002) was conducted to support dose selection. There was some indication that nausea and vomiting occurred more frequently in the higher dosing cohorts (400 and 600 mg TID regimens).

**B. 2.2 CNAB 2002**

CNAB 2002 was a 24 week monotherapy dose-finding and activity study. Treatment-naive subjects were allowed to switch to combination therapy using specified criteria for loss of, or failure to achieve, treatment effect. Sixty subjects entered with median baseline HIV RNA levels of 5.0 log<sub>10</sub> copies/mL and median baseline CD4 counts of 360 cells/mm<sup>3</sup>. Sixty-eight percent met the criteria for CDC class A, and 28% for CDC class B. Median HIV RNA changes from baseline are shown in Table 2 in an "as treated" analysis, which demonstrates the viral load response in subjects remaining on monotherapy for the duration of the trial.

**Table 2: Median HIV RNA log<sub>10</sub> change from baseline in Study CNAB 2002**

	100 mg BID n=20	300 mg BID n=20	600 mg BID n=20
Baseline HIV RNA	4.89	4.94	5.04
Week 4	-0.63 (n=20)	-1.60 (n=19)	-1.61 (n=19)
Week 12	-1.00 (n=11)	-1.25 (n=14)	-2.01 (n=13)
Week 24	-0.57 (n=2)	-1.01 (n=8)	-2.11 (n=7)

After the 4 week visit, because of the significant difference in viral load responses in the 100 mg group compared with other two dosing groups, all subjects in the 100 mg cohort were switched to 300 mg, along with the addition of ZDV and 3TC. Statistical significance was not demonstrated in the differences seen between the 300 mg and 600 mg groups.

CD4 responses at 4 weeks were + 27 cells/mm<sup>3</sup> in the 100 mg group, + 89 cells/mm<sup>3</sup> in the 300 mg group, and + 134 cells/mm<sup>3</sup> in the 600 mg group. These differences were significant for the comparison of the 100 mg dose with the other two doses, but not significant for the comparison of the 300 and 600 mg doses.

Adverse events are shown in Table 3.

**Table 3: Adverse events in Study CNAB 2002**

	100 mg BID (n,%)	300 mg BID (n, %)	600 mg BID (n, %)
Nausea	4 (20)	5 (25)	8 (40)
Malaise and fatigue	2 (10)	4 (20)	11 (55)
Headache	5 (25)	7 (35)	4 (20)
Diarrhea	7 (35)	5 (25)	2 (10)
Fever/chills	3 (15)	1 (5)	4 (20)
GI discomfort/pain	0	1 (5)	4 (20)
Nausea and vomiting	2 (10)	2 (10)	2 (10)
Dizziness	1 (5)	1 (5)	4 (20)

Two subjects in each group experienced grade 3 elevations of triglycerides. Six serious adverse events were reported from this study, two in each dose group. There were two cases of hypersensitivity reactions, documented by re-challenge.

**B.2.3 Conclusions from CNA A 2001 and CNAB 2002**

Results of studies CNA A 2001 and CNAB 2002 provided short-term, non-comparative evidence of the antiviral efficacy of abacavir as monotherapy and in combination with zidovudine in treatment-naive HIV-infected patients.

The results of these two studies were the basis for choosing a dose to carry into the Phase 3 adult studies. Dosing regimens of at least 300 mg BID demonstrated antiviral activity. The 600 mg BID and 400 mg TID regimens appeared on inspection to have somewhat more antiviral activity, but the comparison of each of these with the 300 mg BID regimen was not statistically significant. In addition, more adverse events were reported from subjects receiving the higher dosage regimens. Based on these results, 300 mg BID was chosen as the dose to be studied in the Phase 3 studies of treatment of HIV infection. It is possible that statistical significance was not demonstrated in the comparisons of the 300 mg BID regimen with higher doses because of small sample sizes. However, very reasonable viral load reductions were obtained with the 300 mg BID regimen, and this regimen appeared to have lower adverse event rates. In the HIV dementia trial a dose of 600 mg BID was chosen based on the prospect that at a higher dose more drug would enter the CNS.

Most studies of nucleoside analogues as monotherapy have demonstrated approximately 0.5 log<sub>10</sub> drop in viral load. These studies demonstrated that abacavir provided an increased antiviral effect as monotherapy compared to other agents of its class.

**B. 3 Clinical implications of preclinical studies**

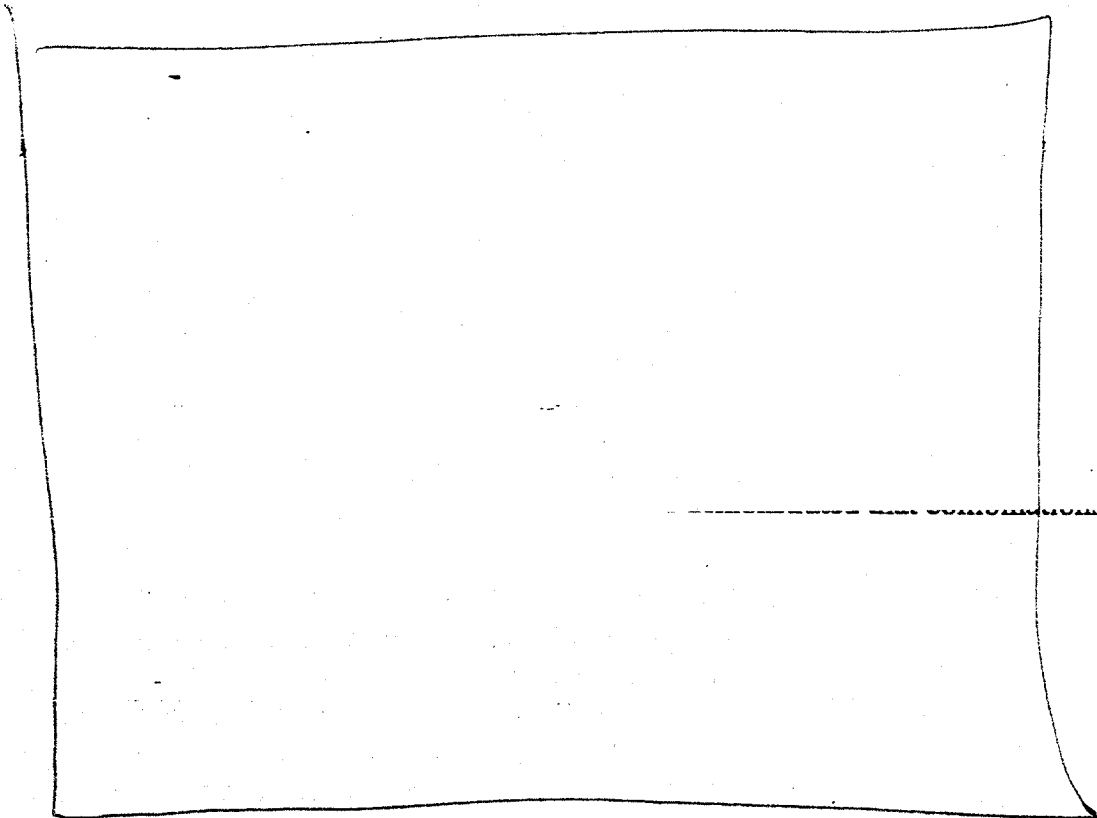
**B. 3.1 Chemistry**

Please refer to Dr. Khambampati's review.

The manufacturing process and sites were found to be acceptable.

**B. 3.2 Microbiology/Virology**

Please refer to Dr. Mishra's review.



**B. 3.3 Pharmacology/Toxicology**

Please refer to Dr. McMaster's review.

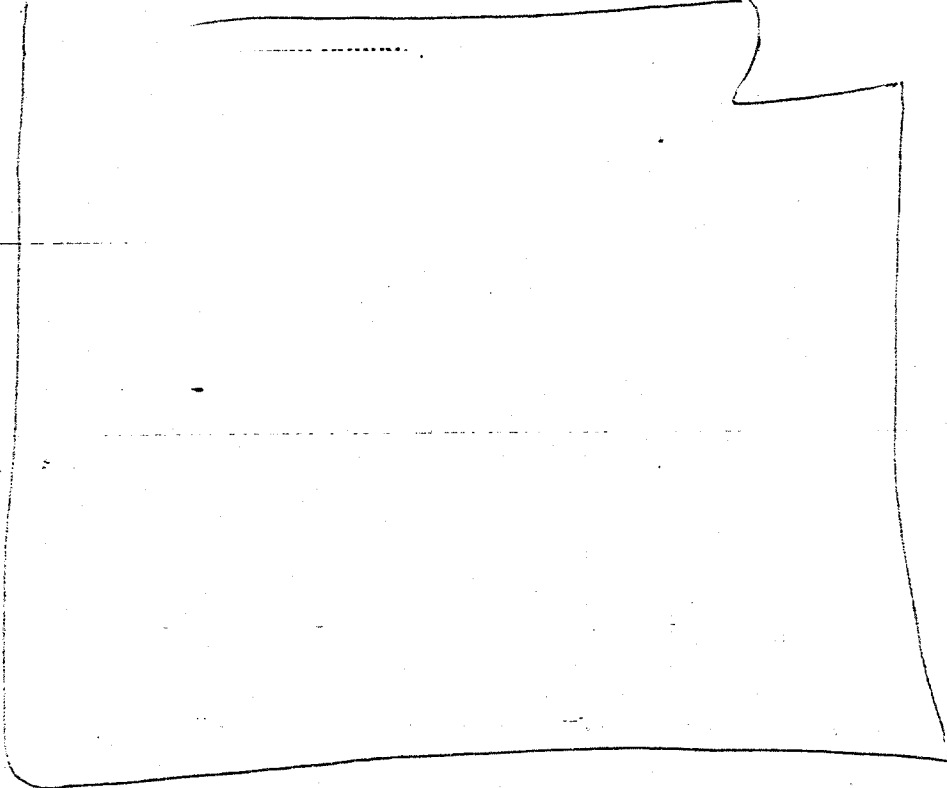
Neither bone marrow toxicity nor lymphocytotoxic effects have been identified in the pre-clinical animal data.

**C. Clinical implications of human pharmacokinetic studies**

Please refer to Dr. Rajagapolan's review.



During the review of pharmacokinetic data, the following clinically important issues were identified:

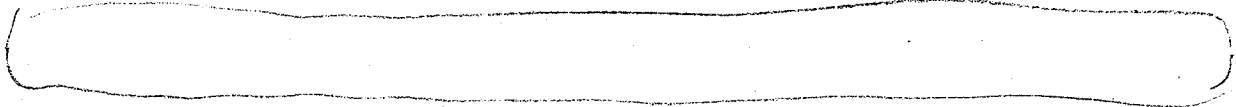


**D. Clinical implications of statistical review**

Please refer to Dr. Elashoff's review. Of note, apparently because of the 16 week CD4 results of an increase of 50 cells/mm<sup>3</sup> in the abacavir group in study 3003, Dr. Elashoff did not recommend that these NDA's be approved. However, his review reflects a statistical viewpoint that does not incorporate results from preclinical studies, the phase 2 studies demonstrating the antiviral activity of abacavir, the knowledge that reconstitution of the CD4 cell populations resulting from antiretroviral therapy is expected to occur over a year or more to therapy, the known problems associated with evaluation and interpretation of CD4 changes in clinical practice and in clinical studies, or the results of subsequent CD4 changes after week 16 in the 3003 study.

**E. Summary of NDA Clinical Section**

This submission contained 16 and 24 week clinical data from studies CNAB 3003 and CNAA 3006; 12 week comparative and 40 week open-label clinical data from CNAB 3001; and



CNA 3006. Upon FDA request, preliminary blinded viral load and CD4 count results from CNAB 3005 were submitted October 10, 1998.

During the review, executive summaries of results from the following studies were submitted: CNAB 3002, ACTG 368, and ACTG 372. Because the results of these studies added little to the conclusions drawn from the principal controlled trials, and because only the executive summaries were available for evaluation, these studies will not be evaluated in this review. Summary information about these studies is provided in Table 5.

The relevant clinical studies reviewed are shown in Table 4.

- Table 4. Summary of Controlled Clinical Trials

Study No.	No. enrolled	Treatment groups	Population	Study design	Primary end point	Duration
CNAB 3003	173	Abacavir+ZDV/3TC vs. Placebo/ZDV/3TC	Treatment-naive adults, CD4 >100	Randomized, double-blind	Viral load below the limit of detection, CD4	16 weeks blinded Ongoing open-label
CNA 3006	205	Abacavir+ZDV/3TC vs. Placebo/ZDV/3TC	Treatment-experienced pediatrics	Randomized, double-blind	Viral load less than 10,000 c/mL, CD4	16 weeks/48 weeks
CNAB 300i	105	Abacavir + background therapy vs. Placebo + background therapy	AIDS dementia	Randomized, double-blind	Neuro-psychological testing	12 weeks blinded Ongoing open-label
CNAB 3005	449	Indinavir/ZDV/3TC vs. Abacavir/ZDV/3TC	Treatment-naive adults, CD4 >100	Randomized, double-blind	Viral load below the limit of detection, CD4	48 weeks blinded

**Table 5. Additional Clinical Trials**

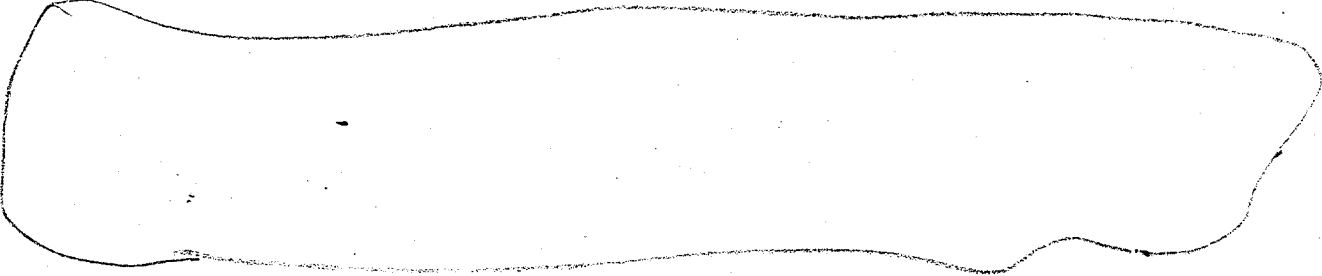
Study No.	No. enrolled	Treatment groups	Population	Study design	Endpoints	Duration
ACTG 330	47	4mg/kg/day or 8 mg/kg/day	pediatrics, treatment- experienced	Pharmacokinetic	PK parameters, activity	12 weeks
CNAB 3008	2113	Abacavir + two new agents	Treatment- experienced	Open-label, expanded access	None	Open-ended
ACTG 368	307	Abacavir +indinavir + efavirenz vs. Placebo + indinavir + efavirenz	Treatment- experienced	Randomized, double-blind		48 weeks
ACTG 372	355	Group A: abacavir + zidovudine + lamivudine + indinavir or, placebo + zidovudine + lamivudine + indinavir Group B: abacavir + efavirenz + adefovir + nelfinavir or placebo or, placebo + efavirenz + adefovir + nelfinavir or placebo Group C: zidovudine + lamivudine + indinavir Group D abacavir + efavirenz + adefovir + nelfinavir	Treatment- experienced	Randomized, double-blind		48 weeks
CNAA 3002	187	Abacavir + background vs. Placebo + background	Treatment- experienced	Randomized, double-blind	Viral load below the limit of detection, CD4	48 weeks

## **F. Principal controlled trials**

### **F. 1. CNA 3003**

"A randomized, double-blind, parallel-group, multi-center trial to evaluate the safety and efficacy of 1592U89 in combination with lamivudine (3TC) and zidovudine (ZDV) versus ZDV/3TC in HIV infected antiretroviral therapy naive subjects with CD4+ cell counts  $\geq 100$  cells/mm<sup>3</sup>"

#### **F. 1.1 Design**



The original study design offered the following switch options to those whose HIV RNA copy number was  $\geq 5,000$  at week 16 or beyond: open-label abacavir + ZDV + lamivudine, open-label abacavir in combination with any another antiretroviral, continuation of blinded treatment, or withdrawal from the trial. Following an amendment to the protocol, the switch criterion was changed to  $\geq 400$  copies/mL of HIV RNA (the lower level of detection of the Roche Amplicor<sup>®</sup> Assay), a second cohort of patients treated with open-label abacavir/ZDV/3TC was added (group B), and the number enrolled into the original cohort (Group A) was reduced to 140 subjects. All subjects have the option of receiving open-label treatment with abacavir after 16 weeks of treatment. The protocol was amended to continue to follow patients through 104 weeks of treatment.

This study was conducted in the United States (12 sites), Belgium (1 site), Spain (6 sites) and the United Kingdom (4 sites). The 16 week comparative phase was conducted between May 6, 1997 and January 26, 1998. Group A patients reached 48 weeks of treatment in October, 1998.

Updates on 24 week and 48 week efficacy and limited safety results were submitted during the course of the review.

**Comments:**

- This review evaluates subjects enrolled in Group A, as only this group provides a controlled comparison.
- With the availability of results from ACTG 320, in which clinical benefit was shown for the combination of ZDV + 3TC + a protease inhibitor (indinavir) over the combination of ZDV + 3TC in adult patients with CD4 counts  $< 200/\text{mm}^3$ , FDA was concerned that the double nucleoside regimen of ZDV/3TC could provide sub-optimal therapy in a portion of the study population. The applicant was aware that FDA questioned whether this study could be conducted for greater than 16 weeks (the duration of blinded treatment without switch options) even with appropriate safeguards.
- Throughout the development of this protocol, FDA expressed concern about the lack of scientific rationale for use of the triple nucleoside combination. This combination has but a single molecular target and all three agents utilize the same mechanism of action. Furthermore, there is the potential for overlapping resistance patterns and toxicities.

**F. 1.2 Study Population/Demographics**

The study was conducted in 173 HIV-infected, treatment-naive subjects with CD4+ counts  $\geq 100$  cells/ $\text{mm}^3$ , 13 years of age and older. Study subjects were 76% male, 54% white, with a median age at entry of 34 years (range 21-61 years). The median viral load at entry was 4.54  $\log_{10}$  copies/mL (range 2.6-6.0), and the median CD4 cell count was 443 cells/ $\text{mm}^3$  (range 109-1289). Most subjects entered with a CDC classification A (71%). With the exception of an imbalance of females between the groups (29% in the ZDV/3TC group, and 18% in the abacavir/ZDV/3TC group), these characteristics were evenly balanced between the treatment groups.

**Comments:**

- The study population represents a healthy group of HIV infected patients.
- The implications of the imbalance in female subjects between the two treatment groups is not known.

**F. 1.3 Planned statistical analysis**

The sample size of 140 subjects enrolled into group A was based on the detection of a difference of 25% in the proportion of patients event-free (viral load  $< 400$  copies/mL) at 48 weeks, with the assumption that 25% would be event-free in the double combination group, and that 50% would be event-free in the triple combination group. It was stated that based on these assumptions there would be 80% power at the 5% level of significance to detect this difference. At 16 weeks, the planned analysis was the AAUCMB for CD4 counts and HIV RNA.

**Comment:**

Increasingly efficacious combinations that achieve more profound changes in viral load and CD4 counts have become available in recent years. In the analysis of efficacy it is now preferable to evaluate the proportions of patients below the limit of detection of the HIV RNA assay, as well as to compare the mean or median changes in CD4 cell count changes from baseline. These analyses were submitted in the NDA, and will be the basis for the evaluation of surrogate marker efficacy.

**F. 1.4 Withdrawal and Compliance**

Of 173 randomized patients, nine patients were randomized but did not initiate treatment. Eighty-seven patients were randomized to the abacavir group, and 86 were randomized to the placebo group. Twelve patients (five in the abacavir group and seven in the placebo group) discontinued the study prior to 16 weeks. Of those who did not complete the study, a total of nine were lost to follow up (four in the abacavir group, and five in the placebo group).

After week 16, 64 patients (76%) in the placebo arm had added abacavir to their treatment regimen, while four patients in the abacavir group switched to open-label therapy.

**F. 1.5 Efficacy Analyses of Surrogate Endpoints**

Antiviral efficacy was assessed by the comparison of the proportions of patients with viral RNA below the level of detection (400 copies/mL). CD4 response was evaluated as median changes over time and from baseline.

Table 6. Summary of Viral RNA and CD4 count results: Study CNAB 3003

Week	Viral RNA [n (%) $\leq$ 400 copies/mL]		CD4 counts (median change from baseline)	
	Abacavir	Placebo	Abacavir	Placebo
16	62 (71)	29 (34)	47	113
24	61 (70)	14 (16)	87	85

**Comments:**

In keeping with recommendations made to all applicants for the statistical analysis of results from studies of antiretroviral agents, subjects who switched treatment were regarded as treatment failures, and this is the analysis that is provided in the package

insert.

Because of the wide variability of the CD4 responses, it was felt that the median change from baseline was the most appropriate evaluation. It should be noted that, although comparisons beyond 16 weeks are complicated due to allowing subjects to switch therapy regardless of viral load responses, the median CD4 counts in the abacavir group are comparable to those found in the small number of subjects with continued response in the dual nucleoside group.

#### **F. 1.5.1 Clinical disease progression**

A total of ten patients experienced disease progression during the first 16 weeks of the study, five in each treatment arm. In the abacavir group, five patients with CDC classification A progressed; four to CDC classification B and one to CDC classification C. In the placebo group, three patients with CDC classification A progressed to CDC classification B, and one patient each with CDC classifications A and B progressed to CDC classification C. Description of these events is not provided in the NDA.

#### **F. 1.6 Safety**

Although 24 week safety information was included in the safety update, 16 week data is presented here (unless otherwise specified) because it provides comparative data.

Three subjects in the abacavir group and four in the placebo group withdrew during the first sixteen weeks for the study for adverse events. Two subjects in the abacavir group withdrew due to hypersensitivity reactions.

##### **F. 1.6.1 Deaths**

A single death in a patient in the abacavir group was reported from this study. The cause of death was described as sudden death due to substance abuse.

##### **F. 1.6.2 Clinical Adverse Events**

Thirteen subjects experienced 15 serious adverse events during the first 16 weeks of the study, six in the abacavir group, and seven in the placebo group. No imbalances in the types of events were noted between the groups. One case of hypersensitivity in a patient receiving abacavir was included.

Selected clinical adverse events are presented in Table 4.

**Table 7. Selected clinical adverse events: Study CNAB 3003**

	Abacavir (n=83)	Placebo (n=81)
Any adverse event	76 (92)	70 (86)
Nausea (n, %)	39 (47)	33 (41)
Malaise/fatigue (n, %)	28 (34)	20 (25)
Headache (n, %)	26 (31)	16 (20)
Nausea and vomiting (n, %)	13 (16)	9 (11)
Sleep disorder (n, %)	6 (7)	4 (5)
Musculoskeletal pain (n, %)	6 (7)	4 (5)

Two patients in each group reported grade 3-4 vomiting. Two patients in the abacavir group and one patient in the placebo group reported grade 3-4 nausea and vomiting. Two subjects in each group reported grade 3-4 headache.

**F. 1.6.3 Laboratory adverse events**

Selected clinical chemistry and hematology changes from baseline are shown in Table 4. Most events were grade 1.

**Table 8: Laboratory adverse event: Study CNAB 3003**

	Abacavir (n=83)	Placebo (n=81)
ALT (n, %)	19 (16)	12 (10)
CPK (n, %)	27 (22)	25 (20)
Hyperglycemia (n, %)	31 (26)	22 (18)
Triglycerides (n, %)	25 (21)	11 (9)
Neutropenia (n, %)	24 (20)	27 (22)
Anemia (n, %)	1 (1)	2 (2)



One patient in each group had a grade 3 ALT elevation. Three patients in the abacavir group and one patient in the placebo group had grade 3 CPK elevations; two patients in the abacavir group and three in the placebo group had grade 4 CPK elevations. One patient in the abacavir group had a grade 3 triglyceride elevation.

A total of five hypersensitivity reactions have been reported from this study, occurring only in subjects receiving abacavir. Reports for two of these were not included in the NDA, but were identified in a submission dated October 28, 1998.

#### **F.1.8 Conclusions**

The results of study CNA 3003 supports the short-term safety and efficacy of abacavir in combination with other antiretroviral agents for the treatment of HIV-infected treatment-naive patients.

In these treatment-naive adult subjects, significantly more subjects who were assigned to the triple nucleoside combination had undetectable viral load at 16 weeks (71% in the abacavir arm vs. 34% in the placebo arm), a finding that supports the antiviral effect of abacavir. Even for the short-term evaluation of efficacy, 16 weeks may not be long enough to allow an adequate description of activity. Therefore, it would be preferable to evaluate viral load responses at 24 weeks. However, since such a significant proportion of patients in the comparator arm switched to open-label treatment with abacavir, no meaningful comparisons of the groups may be made beyond 16 weeks. The 48 week data from this study will be useful to support the safety of abacavir and will provide non-comparative efficacy data. Evidence for the comparable durability of antiviral response will require the evaluation of results of other longer-term studies.

While a CD4 response was demonstrated in the abacavir group, at each time point up to 16 weeks, the CD4 responses of subjects receiving the triple nucleoside regimen were lower than those receiving the dual nucleoside combination. Even though this comparison was not statistically significant ( $p=0.09$ ), these results were troubling. The applicant's analysis of this result did not find a statistically significant difference between the groups, most likely because of the wide variability of the CD4 data. However, FDA believed this result to be worrisome, particularly in light of the known limited efficacy of the comparator group. Statistical analyses of the CD4 findings within study 3003 demonstrated that the results were consistent regardless of the patient characteristics evaluated (viral load strata, CD4 strata, gender and race) (See Dr. Elashoff's review).<sup>1</sup>

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<sup>1</sup>A complete discussion of the potential for CD4 toxicity related to abacavir therapy is found in the conclusions (Section I.).

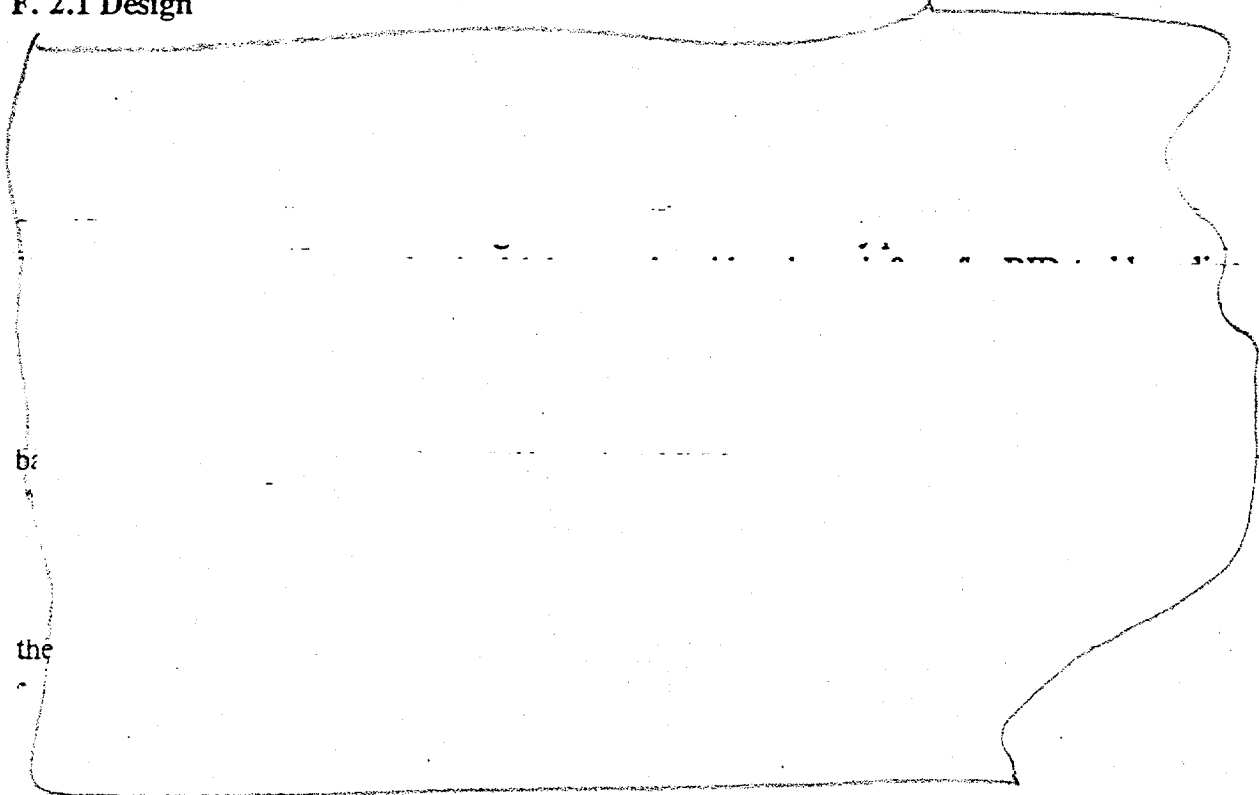
Nausea, nausea and vomiting, malaise/fatigue and headache were reported more frequently in the abacavir group. Laboratory abnormalities associated with abacavir treatment included elevation of LFT's and CPK, hypertriglyceridemia, and hyperglycemia. Grade 3-4 clinical and laboratory adverse events were infrequent.

Five hypersensitivity reactions to abacavir were identified in this study of relatively healthy, treatment-naive subjects.

#### F. 2. Study 3006

"A double-blind, randomized, multicenter trial to evaluate the safety and efficacy of the combination of 1592U89/zidovudine (ZDV)/lamivudine (3TC) versus the combination of zidovudine (ZDV)/lamivudine (3TC) in HIV-1 therapy-experienced pediatric patients" (CNA 3006).

#### F. 2.1 Design



This study is being conducted at 28 centers in the United States and one in Panama. The study opened May 15, 1997, and week 16 evaluations were completed by 26 January, 1998.

An update on 24 week safety and efficacy was submitted during the course of the review.

**Comment:**

FDA requested that children with CD4 percentages less than 15% (a population corresponding to adults with CD4 counts < 200 cells/mL) not be allowed to enter the study in order that they not be randomized to less than optimal therapy.

**F. 2.2 Study population/Demographics**

Two hundred and five pediatric subjects between the ages of 0.6 and 13 years were enrolled (median age 5.4 years). Study subjects were 56% female, 50% Black, and 30% Hispanic. Proportions with each CDC classification were 39% mildly symptomatic (A), 32% moderately symptomatic (B), and 23% severely symptomatic (C). The median baseline viral load was 4.60 log<sub>10</sub> copies/mL HIV RNA (range 2.6-6.45). Twenty-one percent entered with a viral load < 10,000 copies/mL. The median CD4 cell count at entry was 690 cells/mL (range 10-6846). The median CD4% was 27.0 % (range 1.2-61.4). Eight percent had received 3-6 months of prior antiretroviral therapy, 18% had received 6 months -1 year, 23% 1-2 years, and 52% more than 2 years. Eighty percent had received zidovudine, and 55% had received lamivudine in the last six months prior to study entry.

Subjects were stratified by prior ZDV/3TC treatment (yes or no). Half the subjects had received ZDV and 3TC in the six months prior to randomization. However, 61 percent of subjects classified as "no prior ZDV/3TC" had received zidovudine in the prior six months (most often in combination with ddI) and 10% had received lamivudine.

Baseline characteristics were evenly balanced between the treatment groups.

**Comment:**

The extensive exposure to nucleoside analogues, particularly zidovudine and lamivudine, predicted limited responses to the combinations studied.

**F. 2.3 Planned statistical analysis**

The sample size, providing 95% power at the 5% level of significance, was based on the detection of a difference of 25% in the proportion of patients event-free (viral load < 10,000 copies/mL) at 48 weeks, with the assumption that 25% would be event-free in the double combination group, and that 50% would be event-free in the triple combination group. At 16 weeks, the planned analysis was the AAUCMB for CD4 counts and HIV RNA, in addition to the proportion of patients who have viral load results below 10,000 copies/mL.

**Comment:**

Given the paucity of viral load data in pediatric HIV infected patients at the time the study was designed, there were no data available to either support or reject the applicant's proposed endpoint of 10,000 copies of viral RNA/mL. We requested analysis

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### F. 2.3 Withdrawal and Compliance

All of the 205 randomized subjects initiated assigned study treatments. Eleven patients in the abacavir group and three patients in the placebo group discontinued the study prior to 16 weeks. Seven patients in the abacavir group and two patients in the placebo group discontinued due to adverse events. One patient in the abacavir group was lost to follow up.

A total of 28 subjects had discontinued prior to 24 weeks; 17 due to adverse events, 11 for other reasons. The treatment assignments for these subjects were not provided.

### F. 2.4 Efficacy Analyses of Surrogate Endpoints

Antiviral efficacy was assessed by the comparison of the proportions of patients with viral RNA below 10,000 copies/mL and below the level of detection (400 copies/mL). CD4 response was evaluated as median changes over time and from baseline. Viral load results were available for both 16 and 24 weeks, while evaluation of the week 24 CD4 response was not evaluable because results from the subjects at the Panama site (n=25) had not been included in the 24 week data submission.

Table 9 summarizes the overall surrogate marker responses, and Table 10 provides viral load responses by the pre-treatment status of subjects (ZDV/3TC in the last 6 months).

**Table 9. Summary of Viral RNA results: Study CNA 3006**

Week	Viral RNA [n (%) ≤ 10,000 copies/mL]		Viral RNA [n (%) ≤ 400 copies/mL]	
	Abacavir	Placebo	Abacavir	Placebo
16	50/102 (49)	36/103 (35)	13/102 (102)	2/103 (2)
24	47/87 (54)	38/89 (43)	12/87 (14)	1/89 (1)

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**Table 10. Viral load analysis by pre-treatment status: Study CNAA 3006**

	No prior ZDV/3TC	
	Abacavir	Placebo
16 weeks	29/52 (56%)	15/52 (29%)
24 weeks	24/43 (56%)	14/42 (32%)
	Prior ZDV/3TC	
	Abacavir	Placebo
16 weeks	21/50 (42%)	22/51 (43%)
24 weeks	23/44 (53%)	24/47 (51%)

The majority of subjects who entered the study with a viral load of less than 10,000 copies/mL HIV RNA remained below that threshold at 16 and 24 weeks.

Twenty-seven (26%) subjects in the abacavir group and eight (8%) in the placebo group had least a 1.0 log<sub>10</sub> or greater drop in viral RNA by 16 weeks.

The median increase from baseline for CD4 counts was 69 cells/mm<sup>3</sup> for the abacavir group and 9 cells/mm<sup>3</sup> for the placebo group. The AAUCMB for CD4 cell count through week 16 was 51 cells/mm<sup>3</sup> in the abacavir group and an 30 cells/mm<sup>3</sup> in the placebo group.

Analysis of the < 10,000 copies/mL viral load results at 24 weeks did not reveal a significant difference between the two groups in the intent to treat population. Comparison of the < 400 copies/mL viral load results at 24 weeks were statistically significant. There was no apparent treatment effect in those who had received ZDV/3TC in the last six months (Table 10). At 16 weeks there was a numeric advantage for CD4 change from baseline in the abacavir group over the placebo group, though this result was not statistically significant; nor was the AAUCMB comparison statistically significant.

**Comment:**

About 20% of the subjects entering this study had a viral load less than 10,000 copies/mL at entry, and were therefore incapable of achieving the protocol-specified endpoint.

**F. 2.5.1 Clinical disease progression**

Two subjects experienced disease progression during the first 16 weeks of the study. One patient in the abacavir group developed recurrent encephalopathy, and one patient in the

placebo group developed MAI infection.

## F. 2.6 Safety

### F. 2.6.1 Deaths

One subject in the abacavir group died secondary to a brain abscess, and one patient died in the placebo group due to acute renal failure/septicemia.

### F. 2.6.2 Clinical Adverse Events

Twenty-nine subjects experienced 48 serious adverse events; 14 subjects in the abacavir group who experienced 25 SAE's, and 15 subjects in the placebo group who experienced 23 SAE's. Two subjects in the abacavir group experienced hypersensitivity reactions; otherwise the types of adverse events were similar between the groups.

Selected clinical adverse events are presented in Table 11.

Table 11. Selected clinical adverse events: Study CNA 3006

	Abacavir (n=102)	Placebo (n=103)
Nausea and vomiting (n, %)	39 (38)	19 (18)
Cough (n, %)	24 (24)	12 (12)
Fever, chills (n, %)	19 (19)	12 (12)
Diarrhea (n, %)	16 (16)	15 (15)
Headache (n, %)	16 (16)	12 (12)
Skin rash (n, %)	11 (11)	8 (8)

One subject in the abacavir group reported grade 3 vomiting. One subject in each group reported grade 4 fever.

In the abacavir group, four subjects discontinued due to vomiting, and two due to hypersensitivity reactions.

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### F. 2.6.3 Laboratory adverse events

Selected laboratory adverse events are presented in Table 12.

**Table 12: Laboratory adverse events: Study CNAA 3006**

	<b>Abacavir (n=102)</b>	<b>Placebo (n=103)</b>
ALT (n,%)	15 (15)	13 (13)
Hyperglycemia (n,%)	18 (18)	9 (9)
Neutropenia (n,%)	34 (35)	37 (38)
Anemia (n,%)	23 (23)	26 (26)

CPK and triglycerides were not evaluated in this study. The majority of these abnormalities were grade 1 or 2. Two subjects in the abacavir group and six subjects in the placebo group had grade 3/4 neutropenia.

### F. 2.9 Assessment of safety and efficacy

The results from study CNAA 3006 provide limited evidence of the short-term efficacy of abacavir used in combination for the treatment of treatment-experienced HIV infected pediatric subjects.

In this treatment-experienced group of pediatric subjects there was minimal antiviral efficacy. FDA believed the protocol-defined endpoint of 10,000 copies/mL to have limited clinical relevance. In addition, the surprisingly high proportion of subjects entering the study with HIV RNA copy numbers at or below 10,000 copies/mL (20% in each group) lessened the ability of this analysis to demonstrate efficacy. While the comparison of the < 400 copies/mL viral load results at 24 weeks was statistically significant, the number of subjects in both groups with this response was too small to be clinically meaningful. However, regardless of which endpoint was analyzed, the abacavir group showed a consistently better viral load response than the placebo group. Subjects entering the study had been extensively exposed to nucleoside analogues and this is likely to have accounted for the low response rates. There were too few subjects with lesser durations of prior nucleoside exposure to determine the duration of previous nucleoside experience that may predict a lack of benefit of abacavir.

Though not statistically significant, at 16 weeks there was a numeric advantage for CD4 change from baseline in the abacavir group over the placebo group.

**Because of the limited benefit described at 16 and 24 weeks, it is unlikely that the 48 week results from this study will provide evidence supportive of the long-term durability of abacavir in treatment-experienced subjects.**

**Nausea and vomiting were associated with abacavir treatment, and resulted in the discontinuation of four subjects.**

**Laboratory adverse events were similar to those seen in study 3003. Notably the incidence of anemia and neutropenia was similar between the treatment groups.**

**Two cases of hypersensitivity were identified and were the cause of treatment discontinuations.**

### **F. 3.0 CNAB 3005**

#### **F. 3.1 Rationale for requesting efficacy data from CNAB 3005**

Efficacy results from CNAB 3003 supported the antiviral efficacy of abacavir, but the limited CD4 responses raised concern that abacavir could have a potentially deleterious effect on CD4 cells. The CD4 responses from CNAA 3006 (or other studies such as CNAB 3001) were not sufficient to confirm or refute the results from CNAB 3003. In addition, the minimal antiviral efficacy demonstrated in CNAA 3006, though not surprising, provided little support for the overall efficacy of abacavir. Therefore, we requested that the applicant submit additional data that could address these problems. Study CNAB 3005, like study CNAB 3003, is being conducted in treatment-naive adults, and was therefore identified as a study likely to provide CD4 responses with which the results of CNAB 3003 could be compared. Furthermore, we believed additional efficacy data to support the application would be necessary to consider approval of abacavir.

On October 10, 1998, in response to our request for additional data, the applicant submitted preliminary 16 and 24 week blinded viral load and CD4 results from CNAA 3005, which is an ongoing 48 week equivalence-design trial conducted with the purpose of supporting the traditional approval of abacavir. While more complete data from this study has been submitted during the course of the review, complete review and analysis of this study will occur when these data are submitted with the traditional approval NDA submission.

#### **F. 3.2 Summary and preliminary efficacy data from CNAB 3005**

This randomized, double-blinded study in 449 therapy-naive patients compares indinavir/ZDV/3TC with abacavir/ZDV/3TC. The planned primary endpoint will be a comparison of the proportion of subjects with viral load at or below the limit of detection at 48 weeks. These results from preliminary 16 week data are summarized in Table 13. The 16 week results are presented, as these were the most complete results.



**Table 13: Preliminary Blinded Results from CNA 3005**

	Viral RNA (proportion < 400 c/mL)		Median Change in CD4 Count (cells/mm <sup>3</sup> )	
	A	B	A	B
16 weeks	62%	65%	+83	+103

**F. 3.3 Preliminary assessment of efficacy**

Preliminary efficacy results from study 3005 supplement the original application by providing a comparison to a combination that represents the current standard of therapy (protease inhibitor plus two nucleoside analogues). In addition, the population is comparable to that of CNAB 3003.

Review of these preliminary data submitted from study 3005 indicate that striking differences between the two active treatment arms were not seen for either the virologic effect or the CD4 response.

While the reasonable CD4 response found in this study is reassuring, we recognize that these are preliminary results from a single study that will require confirmation, and, that results from the completion of this and other studies will provide the wider experience required to more adequately address questions about CD4 responses.

**G. Additional Clinical Trials**

**G. 1. CNAB 3001: AIDS dementia**

"A Phase III, randomized, double-blind, multicenter study to evaluate the safety and efficacy of 1592U89 in HIV-1 infected patients with AIDS Dementia Complex".

The applicant's rationale for conducting this study was based on the pre-clinical observations that penetration of abacavir into monkey CSF and rat brain was comparable to that of zidovudine. CSF samples for abacavir determination had been obtained from four patients receiving 200 mg of abacavir TID, and CSF/plasma ratios were found to average 0.18 (which is comparable to zidovudine). In addition, *in vitro* data suggested that abacavir had better inhibitory activity in macrophages than in peripheral blood lymphocytes. Finally, this study could provide clinical endpoint data that would potentially be the basis for an AIDS dementia indication.

**G. 1.1 Design**

Study CNAB 3001 was an international randomized, double-blind, placebo-controlled parallel-

group trial designed to evaluate the benefit of adding abacavir to current antiretroviral therapies in AIDS dementia complex patients as determined by performance in standardized neuropsychological tests. Subjects were stratified during the pre-entry period into group A if their existing therapy contained zidovudine or into group B if their regimen did not contain zidovudine. Patients were treated for 12 weeks with either abacavir or placebo, in addition to their usual antiretroviral regimen. The dose of abacavir was 600 mg every 12 hours. Patients completing 12 weeks were offered 40 weeks of open-label treatment with abacavir. Patients deemed to be progressing on treatment (defined as progressing by one stage on the MSK scale, and confirmed by an endpoint committee) after six weeks of therapy were offered open-label treatment with abacavir.

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**Comment:**

We believed it unlikely that 12 weeks would be adequate to evaluate the efficacy of abacavir for the condition of AIDS-related dementia. The applicant was encouraged to extend the study for a longer period of time, given that we had not been provided with information supporting a shorter duration of study.

**G. 1.2 Population**

The study was conducted in 105 HIV-infected patients with AIDS dementia complex (as defined by the American Academy of Neurology), age  $\geq 18$  and  $\leq 65$  years, receiving a stable antiretroviral regimen for at least eight weeks. Study subjects were 98% male, 81% Caucasian and the median age was 41 years. The median viral load at entry was 3.72  $\log_{10}$  copies/mL in the abacavir group, and 4.5  $\log_{10}$  copies/mL in the placebo group. Twenty-three percent of subjects in the abacavir group and nine percent in the placebo group had undetectable viral loads at entry. The median CD4 cell count was 150 cells/mm<sup>3</sup> (range 7-915) in the abacavir group, and 188 cells/mm<sup>3</sup> (range 5-800) in the placebo group. The baseline Memorial Sloan Kettering (MSK) score was 47 in the abacavir group, and 49 in the placebo group. These scores represent mild to moderate dementia. All patients were CDC class C. The majority of patients were receiving triple therapy that included a protease inhibitor.

Baseline characteristics were well balanced between the groups, with the exception of viral load, which was lower in the abacavir group.

**Comment:**

The large proportion of patients receiving triple therapy that included a protease inhibitor reflected the growing use of protease inhibitors that took place as this study was enrolling.

**G. 1.3 Withdrawal and Compliance**

Fifty-two patients were randomized to the abacavir group, and 53 patients were randomized to the placebo group. Three patients in each group withdrew prior to completing the baseline

**G. 1.5.2 Clinical Adverse Events**

Selected clinical adverse events are presented in Table 14.

**Table 14. Selected clinical adverse events: Study CNAB 3001**

	<b>Abacavir (600 mg BID) (n=49)</b>	<b>Placebo (n=50)</b>
Nausea and vomiting (n, %)	23 (47)	16 (32)
Malaise/fatigue (n, %)	12 (24)	8 (16)
Headache (n, %)	8 (16)	15 (30)
Neuropathy (n, %)	8 (16)	6 (12)
Disorder of lipid metabolism (n, %)	6 (12)	4(8)
Skin rash (n, %)	4 (8)	6 (12)

Four subjects in the placebo arm, and two in the abacavir arm experienced grade 3/4 headache. Four subjects in the placebo arm and two in the abacavir arm experienced grade 3/4 nausea. Three subjects in the placebo arm and one in the abacavir arm experienced grade 3/4 malaise and/or fatigue.

Two subjects experienced hypersensitivity reactions (one described above under "Deaths").

**G. 2.6.3 Laboratory adverse events**

Laboratory adverse events are presented in Table 15.

**Table 15: Laboratory adverse events: Study CNA 3006**

	<b>Abacavir (n=102)</b>	<b>Placebo (n=103)</b>
ALT (n, %)	15 (15)	13 (13)
Hyperglycemia (n, %)	18 (18)	9 (9)
Neutropenia (n, %)	34 (35)	37 (38)
Anemia (n, %)	23 (23)	26 (26)

CPK and triglycerides were not evaluated in this study. The majority of the laboratory

evaluations. There were 16 premature discontinuations: seven in the abacavir group and nine in the placebo group. Reasons for discontinuation were balanced between the groups.

#### **G. 1.4 Efficacy Analyses**

##### **G. 1.4.1 Results of neuropsychological testing**

At week 12, both groups had improved. The change from baseline to week 12 of the summary neuropsychological Z score resulted in a median increase in summary scores of 0.76 in the abacavir group, and 0.63 in the placebo group ( $p=0.735$ ).

##### **G. 1.4.2 HIV RNA and CD4 results**

No changes from baseline viral load were detected at 12 weeks in either group. More patients in the abacavir group had undetectable viral loads at 12 weeks (17/37, 46%) than in the placebo group (5/39, 13%). Median CD4 cell count changes from baseline at week 12 were 9 cells/mm<sup>3</sup> in the abacavir group, and -1 cell/mm<sup>3</sup> in the placebo group.

#### **Comment:**

Subjects in the abacavir group entered the study with a lower viral load at baseline than those in the placebo group (3.72 log<sub>10</sub> c/mL vs. 4.5 log<sub>10</sub> c/mL), and more subjects in the abacavir group entered the study with undetectable HIV RNA at baseline than in the placebo group (23% vs 9%). This study did not have sufficient power to demonstrate differences in virologic endpoints.

#### **G. 1.5 Safety**

##### **G. 1.5.1 Deaths**

Two deaths occurred during the first 12 weeks of the study, one in each group. Cause of death for the patient in the placebo group was listed as anemia and respiratory arrest. The subject in the abacavir group developed fever and headache one week after initiating abacavir. He subsequently experienced seizures and cardiopulmonary arrest. Evaluation for the etiology of the symptoms experienced by this patient was not revealing. The investigator related the events to therapy with abacavir.

#### **Comment:**

Given the lack of an alternative etiology, the symptoms and typical time course of the event, an abacavir hypersensitivity reaction cannot be excluded as the etiology of the illness that preceded the death of the patient in the abacavir group.

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abnormalities were grade 1 or 2. Two subjects in the abacavir group and six subjects in the placebo group had grade 3/4 neutropenia.

#### **G. 1.6 Assessment of safety and efficacy**

**Study CNAB 3001 does not support the efficacy of abacavir added to background therapy for the short-term treatment of AIDS dementia. Results from this study do provide safety data at a higher dose of abacavir (600 mg BID).**

Subjects on both treatment arms demonstrated small and similar neuropsychological improvements after 12 weeks on assigned treatment. A modest increase in the proportion of subjects with undetectable viral load was demonstrated in the abacavir group; however, subjects in this group entered the study with a lower viral load than those assigned to the placebo group. A CD4 response was not demonstrated in either group. It should be noted, given the concern about the possibility of CD4 toxicity related to abacavir treatment, that CD4 counts remained stable during the treatment period in this group of patients with AIDS.

Nausea and vomiting, and malaise and fatigue occurred more frequently in subjects assigned to receive abacavir. Notably, the adverse event profile at this higher dose was not unlike that described in the other phase 3 studies. Mild elevations of blood glucose were more frequent in the abacavir group.

Based on the results of this study, the applicant has not sought an indication for AIDS dementia.

#### **G.2. CNAB 3008: Expanded access protocol**

This was an open-label, multicenter study in patients > 13 years of age with CD4 counts less than 100 cells/mm<sup>3</sup> and HIV RNA > 30,000 copies/mL while receiving currently acceptable antiretroviral therapy, and who were intolerant to previous protease inhibitor therapy or had experienced failure to at least two previous treatment regimens. Patients were evaluated at baseline and monthly in order to remain on the study. Safety information was collected each month. Viral load results were obtained for the first two months after initiation of abacavir in the first 200 patients.

At the time of NDA submission, 2113 patients were included in the interim report. The mean age at enrollment was 41 years (range 17-70), 91% were male, and 77% were white. The mean CD4 count at baseline was 35 cells/mm<sup>3</sup>, and the mean log<sub>10</sub> HIV RNA was 5.35 copies/mL. Thirty-two percent initiated abacavir in combination with another nucleoside reverse transcriptase inhibitor and a protease inhibitor, and 30% initiated abacavir in combination with a nucleoside reverse transcriptase inhibitor, a non-nucleoside reverse transcriptase inhibitor, and a protease inhibitor. Six percent were treated with abacavir as

monotherapy. The mean decrease in  $\log_{10}$  HIV RNA in the first 200 patients was -0.29 copies/mL (range +1.38 to -3.86) at two months. Twenty-five percent of patients experienced a 0.5  $\log_{10}$  decrease in HIV RNA at two months; 10% of patients experienced a 1.0  $\log_{10}$  HIV RNA response, and 5% were below the limit of detection. Patients who experienced responses of  $> 1.0 \log_{10}$  (n=15 of 98 evaluated) all had isolates susceptible to abacavir at baseline by recombinant virus assay. CD4 responses were not provided.

There were 68 deaths reported as serious adverse events (SAE). There were 51 deaths (2.4%) reported on the record of death page of the CRF. Thirty-six of these were attributed to HIV disease progression. The applicant reported one death due to a hypersensitivity reaction; FDA identified six deaths as possibly attributed to hypersensitivity reactions.

A total of 262 patients experienced at least one SAE. Thirty-three cases of abnormal liver function tests and twelve cases of abnormal enzyme levels were reported. There were 14 skin rashes and 10 cases of allergy and allergic reaction. In addition there were 13 cases of pancreatitis. Hypersensitivity reactions in this study are described below.

Adverse events described as non-serious were reported by 66% of patients. These events were similar to those described in the phase 3 studies (nausea, vomiting, diarrhea, rash, malaise and fatigue, and headache).

**Comment:**

Overall, viral load response to treatment with abacavir in this pre-treated population with low CD4 counts and relatively high viral loads at baseline was minimal. Since most patients had prior exposure to nucleoside analogues, it is likely that baseline resistance to abacavir, as well as resistance to other components of the combinations used, was responsible for this lack of response.

## **H. Hypersensitivity Reactions**

### **H. 1. Definition**

The most serious adverse event that has been associated with abacavir treatment has been hypersensitivity reactions. These reactions were noted early in the development of abacavir. Fever, rash, and gastrointestinal complaints are the most frequently reported symptoms, though cases have been reported in the absence of each of these. Initial symptoms were often described as "flu-like", or patients were suspected to have sepsis or other generalized infectious syndromes.

The exanthem, when present, is most often generalized, maculopapular, erythematous, and may be pruritic. Urticaria and photosensitivity have been reported. Enanthems such as conjunctivitis and oral ulceration have occurred, but appear to be less common. Cases of Stevens-Johnson syndrome have also been described. Gastrointestinal symptoms include nausea, vomiting, diarrhea, anorexia, and abdominal pain. Myalgia, arthralgia, paresthesia,

chills and rigors, lymphadenopathy, hepatomegaly, splenomegaly, and edema were reported, though less commonly.

Unrecognized reactions resulting in continued dosing were associated with accumulation and worsening of symptoms. More severe reactions have included anaphylaxis, severe hypotension requiring pharmacologic support of blood pressure, respiratory symptoms and respiratory failure requiring intubation and mechanical ventilation, liver failure and renal failure. Re-challenge has been associated with the rapid return of symptoms, and symptoms after re-challenge are usually more severe.

Eight deaths were identified by FDA as possibly associated with hypersensitivity reactions. Two of these occurred after re-challenge.

Laboratory abnormalities associated with these reactions have included increased liver function tests, elevations of creatine phosphokinase and serum creatinine, and neutropenia and lymphopenia.

The time between onset of the reaction and the initiation of abacavir is usually less than six weeks. Cases have occurred after months of dosing, but these appear to be uncommon. Reactions have also occurred after one or two doses of abacavir.

Risk factors have not been identified for this adverse event. Cases have occurred in subjects with all stages of HIV infection, in both pediatric and adult patients, and without obvious predilection for race.

Discontinuation of abacavir usually results in resolution of symptoms, but, as discussed further below, deaths have occurred in relationship to hypersensitivity reactions.

## H. 2. Incidence

The applicant has reported that approximately 3% of patients in clinical trials of abacavir have been recognized to develop these reactions. The applicant identified cases by searching their electronic database using the following definition:

1. Fever plus nausea, vomiting, malaise, or rash; or
2. Cases reported as allergic or hypersensitivity reactions;
3. Occurrence within the first six weeks of dosing.

Cases so identified were then reviewed and included as cases of hypersensitivity if an alternative diagnosis was not provided.

Due to the nature of the safety reporting, at this time FDA does not have complete access to the safety database used by the applicant to define the incidence of hypersensitivity reactions. Therefore, we have been unable to verify the incidence (or the symptomatology, time course, or risk factors) reported by the applicant using their methods.

FDA identified cases by review of all case narratives for serious adverse events included in the NDA. Hypersensitivity cases were identified by the following: the occurrence of typical symptoms described above in a patient receiving abacavir, recurrence of symptoms with re-challenge, the evolution of symptoms with continued dosing, or identification of the case as an allergic or hypersensitivity reaction by the reporter, along with lack of convincing alternative diagnoses.

#### H. 2.1. Incidence in controlled studies of abacavir

The following table provides rates of hypersensitivity identified in the controlled studies.

**Table 16 : Hypersensitivity reactions in controlled studies of abacavir**

Study number	Number receiving abacavir	Cases identified by applicant	Cases identified by FDA	Rate (FDA analysis)
2001	79	3	3	3.8%
2002	60	3	4	6.7%
2003	32	0	0	0
2004	78	4	4	5.1%
3001	48	2	3	6.3%
3003	85	4	5	5.9%
3006	100	2	3	3.0%
3002	91	3	5	5.5%
Total	573	21(3.6%)	27	4.7%

In general, the cases identified by the applicant and FDA appeared to be the same cases, though FDA included six cases not identified by the applicant.

A comparison of cases from study 3005 could not be included in the above table, because all the serious adverse event case report narratives from that study have not been submitted and reviewed. The applicant has reported 13 cases from that study. The number of subjects reported to be assigned to the abacavir group is 225. Assuming that the database for this study is fairly complete, the rate reported by the applicant would appear to be 5.7%.



**Comment:** Though these studies are small (with the exception of study 3005), it is notable that the rates of hypersensitivity reported are generally quite consistent across the studies and over time.

#### **H. 2.2 Incidence in the expanded access study, 3008**

In order to identify cases that could be associated with a known denominator in the expanded access study (3008) all cases occurring prior to the cut-of date of March 13, 1998 (the cut-off date of the original NDA submission) were identified. With a denominator of 1,644 as of that date, FDA identified 49 cases by review of the case narratives. The applicant identified 42 cases utilizing their method (described above). Comparison of the case numbers revealed that 31 cases had been identified by both methods. In order to obtain a conservative estimate of incidence in this uncontrolled study, 11 cases identified by the applicant, but not identified by FDA review of the case narratives, were added to the 49 cases already identified by FDA, to give a total of 60 cases, for an incidence of about 3.7%.

**Comment:** Under reporting of adverse events is typical of expanded access studies. When the increased severity of these reactions upon re-challenge was detected in October of 1997, investigators in all studies were informed about the importance of avoiding re-challenge, and the potential for fatal reactions. Wallet cards were provided to subjects that described the common symptoms of hypersensitivity related to abacavir treatment, instructions for seeking care, and the potential for fatal reactions. In addition, the agency requested that all potential cases of hypersensitivity be reported as serious adverse events. It is difficult to assess the impact on reporting of the information provided to investigators about hypersensitivity reactions during the conduct of this study.

#### **H. 2.4. Deaths associated with hypersensitivity reactions**

The applicant identified two deaths as associated with hypersensitivity reactions. However, eight deaths were identified upon FDA review of the case event narratives that were associated with hypersensitivity reactions. Two of these deaths occurred after re-challenge. Deaths were identified as potentially associated with hypersensitivity reactions by virtue of either the identification of characteristic signs, symptoms and clinical course without an adequate alternative explanation, or investigator designation of the death as a potential case of hypersensitivity. Six of these deaths took place in patients enrolled in 3008, the expanded access program.

Case event narratives for these deaths are provided in the Appendix. These cases were presented by the applicant to the Antiviral Advisory Committee on November 2, 1998.

**Comment:**

Given the co-morbidities of the population studied, the considerable overlap between the symptoms of hypersensitivity and other common syndromes experienced in this

population (making rapid recognition of hypersensitivity difficult), and the potential severity of these reactions, it is not unexpected that some hypersensitivity reactions have resulted in death.

## **H 2.5 Conclusions**

Hypersensitivity reactions that may result in death if unrecognized are the most serious adverse reaction associated with abacavir therapy identified during clinical trials of abacavir. Recognition of hypersensitivity reactions that results in prompt, permanent discontinuation of abacavir will be critically important to prevent morbidity and mortality in patients treated with abacavir.

The obvious overlap of the signs and symptoms of hypersensitivity reactions with other common syndromes and with reactions to other commonly used drugs in this population complicates accurate diagnosis of these events. In particular, rash is associated with several commonly used antiretroviral agents, such as nevirapine and efavirenz, as well as with the unapproved protease inhibitor amprenavir (under development by Glaxo Wellcome). It appears that discontinuation of efavirenz or amprenavir may not be necessary when rash occurs in association with these agents, and rashes associated with use of nevirapine, though usually treatable, have in some cases resulted in SJS and death. Because rash may herald a hypersensitivity reaction to abacavir, and because the rashes associated with these agents may be indistinguishable, it is likely that discontinuation of abacavir when rash occurs will be vital to avoiding serious outcomes, even though the rash may not be due to abacavir. Likewise, because the outcome may be so serious if abacavir is continued, the occurrence of flu-like or other similar syndromes will probably mandate discontinuation of abacavir in individuals who do not have hypersensitivity to abacavir. Confirmation by re-challenge will not be possible in these individuals because of the risk of more severe reactions associated with re-challenge.

FDA and the applicant have devised the following in order to address the need to provide wide dissemination of information about hypersensitivity reactions to patients and prescribers.

- A Medication Guide for abacavir was written in accordance with the recently approved Medication Guide regulations. It highlights information about hypersensitivity as well as providing information about the proper use of the drug and other safety information and will be provided to patients with each prescription of abacavir.
- In addition, a wallet warning card that briefly describes hypersensitivity reactions as well as the need to discontinue abacavir and seek medical advice if patients experience symptoms compatible with a hypersensitivity reaction will be provided to patients with each prescription of abacavir.
- Abacavir labeling will include a boxed warning with a brief description of these reactions, with a more detailed description included in the warnings and adverse events sections. The precautions section will include information about

**hypersensitivity reactions that should be provided to patients, and the dosage and administration section indicates that the Medication Guide and wallet warning card are to be provided to patients with each prescription.**

**Further study of these hypersensitivity reactions will be essential. In order to fully characterize these events, the applicant has committed to a comprehensive plan to study abacavir hypersensitivity reactions as a phase 4 commitment. The elements of this plan are as follows:**

- 1. Prior to accelerated approval, the applicant will include a toll-free 1-800 number in abacavir labeling to facilitate reporting of post-marketing hypersensitivity reactions.**
- 2. As an ongoing effort beginning immediately after accelerated approval, the applicant will conduct a review of the safety-related information in the professional labeling, Medication Guide, and Warning Card in order to assure that such labeling remains current and effectively conveys the importance of the warnings.**
- 3. Within 45 days after accelerated approval, the applicant will submit a draft protocol for a prospective, population-based epidemiologic study to evaluate abacavir hypersensitivity reactions. In addition, the applicant will continue to collect and describe abacavir hypersensitivity reactions occurring in ongoing clinical trials.**
- 4. Within 60 days after accelerated approval, the applicant will submit a proposal for the study of the biologic mechanism/immunologic basis of hypersensitivity reactions to abacavir sulfate.**
- 5. Within 60 days after accelerated approval, the applicant will submit a concept sheet for a labeling comprehension study for subjects reading the Medication Guide and Warning Card. Following consultation with experts, complete protocol for this study will be submitted to \_\_\_\_\_**

## **I. Overall assessment of the short-term efficacy and safety of abacavir**

### **I. 1. Effect of abacavir on CD4 responses**

Several lines of reasoning have contributed to the conclusion that at this time it appears unlikely that abacavir has a deleterious effect on CD4 responses. First is the danger inherent in drawing far-reaching conclusions from a single study that attempts to evaluate complex biological systems. Study 3003 was somewhat small and the CD4 data were much more variable than has been the case in other studies evaluating CD4 responses in similar patient groups. The median baseline CD4 counts were high; wider variability may be expected in patients with higher CD4 counts. Little is known about responses to therapy in subjects with relatively preserved CD4 counts. The response in the placebo group was probably spuriously high, providing even more contrast to the comparison. (The CD4 change from baseline in the placebo group was 73 cells/mm<sup>3</sup> at week 12, 113 at week 16, and 85 at week 24.)

The second line of reasoning explored the biological plausibility of a toxic effect of abacavir on

CD4 cells. A more general effect on bone marrow, manifest as anemia and neutropenia, has been associated with other nucleoside analogues, particularly zidovudine. Bone marrow suppression, greater than that associated with the combination of zidovudine and lamivudine, was not noted in study 3003, nor has it been identified in other phase 2 or 3 clinical studies. Bone marrow suppression was not noted in the preclinical animal studies, nor was a toxic effect on bone marrow-derived cells identified.

A specific toxic effect on CD4 has apparently been associated with ddC. At 3-10 times the human dose, reversible dose-related decreases in CD4, CD20 and red blood cells were associated with ddC administration to rhesus monkeys.<sup>2</sup> Adverse effects on CD4 cells have apparently been described in clinical trials of ddC, along with neutropenia. While no similar pre-clinical study of abacavir has been conducted, negative effects on either CD4 or white cells were not identified in any of the phase 2 trials of abacavir.

At our request for further phase 3 data in treatment-naive patients, we requested preliminary efficacy results from study 3005. Though blinded, both treatment arms demonstrated reasonable CD4 responses at 16 weeks. The antiviral effect of abacavir in treatment-experienced patients is minimal and positive CD4 responses from studies in this population were not seen. However, one might expect a negative effect to manifest in this population, as bone marrow effects are usually more pronounced in advanced patients. Such negative effects were not identified in multiple studies in advanced patients.

And finally, though FDA has not verified these results, the 48 week CD4 results from study 3003 showed a 150 cell/mm<sup>3</sup> and 158 cell/mm<sup>3</sup> increase from baseline in the abacavir and placebo groups respectively. It should be noted that nearly all subjects in the placebo group had added abacavir along with other antiretroviral agents after 16 weeks, and that all but four subjects in the abacavir group remained on assigned treatment.

Based on the reasoning outlined above, we believe it unlikely that a significant deleterious effect of abacavir on CD4 cells has been identified at this time. Analysis of the studies submitted for traditional approval will provide additional data to support or refute these conclusions.

## I. 2. Dose

The results of two Phase 2 studies supported the choice of 300 mg BID as the dose selected for study in the phase 3 trials, based on both antiviral activity and the safety profile. The efficacy of this dose was confirmed in the phase 3 trials in treatment-naive subjects. A dose of 600 mg BID was studied in study 3001. Although more adverse events occurred at this dose in the phase 2 trials, the adverse event profile in this study was fairly similar to that seen in studies using the

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<sup>2</sup>Taylor L.D., Binienda, Z, Schmued L, Slikker W., "The effect of dideoxycytidine on lymphocyte subpopulations in nonhuman primates", *Fundamental and Applied Toxicology* 1994; 23, 434-438.

lower dose. The 300 mg BID dose appears to be efficacious, though the possibility remains that a 600 mg BID dose, or TID dosing might improve efficacy without significantly increasing adverse events.

### **I.3. Efficacy and safety conclusions**

In support of the efficacy and safety of abacavir in combination with other antiretroviral agents for the treatment of HIV infection in adults and children, the applicant has submitted the results of three adequate and well-controlled surrogate endpoint trials. Safety experience was also supported by results from phase 2 trials and a large expanded access study.

Sixteen week results from study CNAA 3003 demonstrated that treatment with abacavir in combination with other antiretroviral agents demonstrated superior antiviral activity when compared to the combination of zidovudine and lamivudine in treatment-naive adults. In addition, 24 week preliminary results from CNAA 3005 demonstrated similar efficacy results when the combination of abacavir with zidovudine and lamivudine was compared to indinavir plus zidovudine and lamivudine in treatment-naive adults. The durability of the surrogate response beyond 24 weeks or the impact of abacavir therapy on clinical disease progression is unknown.

The short-term results from study CNAA 3006 demonstrated limited efficacy for abacavir in combination with other antiretroviral agents in the treatment of treatment-experienced subjects. Results from other studies in similar populations (CNAB 3008, CNAB 3002, ACTG 330), as well as evaluation of resistance patterns identified in patient viral isolates, support this conclusion. Based on knowledge about the resistance profile of abacavir, it is likely that extensive prior exposure to other nucleoside analogues may predict the lack of benefit of abacavir in these patients. There is not adequate information available at this time to determine the duration of prior exposure to these agents to predict which patients may not benefit from abacavir.

The most concerning adverse event associated with abacavir treatment is a hypersensitivity reaction, reported in at least 5% of subjects enrolled in clinical trials of abacavir. If unrecognized or severe, hypersensitivity reactions have resulted in deaths. Dissemination of information about this reaction will include a boxed warning, descriptions in the warnings, precautions, and adverse events sections in the label, and provision to patients of a Medication Guide and wallet warning card with each new prescription of abacavir. Commitment by the applicant to comprehensive study of this serious adverse event is outlined in the phase 4 commitments.

Other adverse events associated with short-term abacavir therapy in the phase 3 clinical trials include nausea and vomiting, headache, and malaise or fatigue. Laboratory adverse events associated with abacavir therapy are generally similar to those associated with other nucleoside analogue agents. Mild elevations of blood glucose were associated with abacavir therapy in three controlled trials. Triglyceride elevations (all grades) were detected more frequently in subjects

receiving abacavir in study CNAB 3003. Conclusions about the long-term safety profile of abacavir cannot be made at this time.

**J. Recommended regulatory action**

Based on the information submitted to NDA 20-977 and NDA 20-978, abacavir 300 mg BID in adult patients and 8 mg/kg BID in pediatric patients should be approved.

**K. Addendum**

NDA's 20-977 and 20-978 were approved on December 17, 1999.

/S/

Therese Cvetkovich, M.D.  
Medical Officer, DAVDP

**Concurrences:**

HFD-530/Division Dir/H Jolson

*HJ*  
10/12/99

**cc:**

- HFD-530/NDA 20-977
- HFD-530/NDA 20-978
- HFD-530/Division file
- HFD-530/Biopharm/Rajagopalan
- HFD-530/Pharm/McMaster
- HFD-530/Micro/Mishra, Iaconno-Connors
- HFD-530/Chem/Khambampati
- HFD-530/MO/Cvetkovich, Martin
- HFD-530/Stat/Elashoff, Flyer
- HFD-530/Project Manager/Truffa

Appendix: Summary reports of deaths associated with hypersensitivity reactions

**Appendix: Deaths potentially associated with hypersensitivity reactions**

**1. # 10074**

This subject died shortly after re-introduction of study drug. Though the initial illness was diagnosed as pneumonia, the presentation was consistent with a hypersensitivity reaction and the work-up for pneumonia was negative. This case was included because of the characteristic presentation.

**2. # 10965**

The investigator believed a hypersensitivity reaction possible, and the description of symptomatology and progression of symptoms is consistent with a hypersensitivity reaction.

**3. # 11084**

Although this case is quite complicated, other reasons for the symptoms were not identified, and the clinical course is consistent with an unrecognized hypersensitivity reaction. This case was included because of the characteristic presentation.

**4. # 08103**

This case represents a death after re-challenge. This case was included because of the characteristic presentation.

**5. # 12097**

Distinction between staphylococcal sepsis and a hypersensitivity reaction is not possible in this case, and given the investigator's clinical suspicion of hypersensitivity, both must be included as possible causes of death.

**6. # 10132**

This death is included because the investigator believed that a drug reaction to study drug was possible.

**7. # 11263**

Although this case is quite complicated, anaphylaxis must be included as a possible reason for the symptoms described. This case was included because of the characteristic presentation.

**8. # 5004**

Because of the negative work-up for the presenting symptoms, hypersensitivity must be considered as a potential cause of this patients symptoms. This case was included because of the characteristic presentation.

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Protocol Id: CNAE3008  
Subject number: 12097  
Treatment number: OPEN  
Case Id: B0053130  
Trial medication and Dose: Abacavir (Caplet - 300mg)

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This 31 year old male patient was receiving oral 1592U89 300mg twice daily for the treatment of HIV infection. Concurrent medication included didanosine, stavudine, nelfinavir, foscarnet, fluconazole and co-trimoxazole. He had a history of multiple previous infectious episodes including tuberculosis, bacterial pneumonia, meningitis and he had suffered two previous episodes of septicaemia, one with Staphylococcus aureus and the second with pneumococcus as recently as a month prior to the reported events. The latter episode was associated with an exacerbation of an underlying neutropenic leucopenia. The patient also had stage C cytomegalovirus (CMV) infection and was currently being treated for a relapse of CMV retinitis with two infusions of foscarnet daily. After about one week's treatment with foscarnet and approximately two months after starting the study medication, his left (infusion) arm became inflamed and he received two tablets of paracetamol. A few hours later, the patient experienced an episode of vomiting and felt feverish (although he did not take his temperature). The next morning the patient took aspirin and his usual medication and went to the out-patient unit for his next infusion of foscarnet. However, the infusion was not done because of suspected thrombophlebitis of the left arm. The physician noticed a generalised rash which had not been present one hour earlier when he had made his initial examination. The study medication and all other medication was stopped and the patient was treated with metoclopramide and chlorpheniramine. The symptoms improved initially and then worsened with the occurrence of dyspnoea in the afternoon. He was then admitted to hospital with severe "acute immunoallergic symptoms" and severe septic shock which were associated with a fever (38.2°C), oedema of the face, bilateral conjunctivitis, tachycardia and an urticarial cutaneous rash on his abdomen and all four limbs. He was treated with aspirin, hydroxyzine, hemisuccinate hydrocortisone and loratadine. The urticarial lesions disappeared during the night but the fever persisted. Early the next morning, the patient became increasingly dyspnoeic and hypotensive (unresponsive to colloid infusion) and he went on to develop cardiorespiratory failure requiring intubation, manual ventilation and external cardiac massage. He did not respond to adrenaline and cardiorespiratory arrest resulted in death. A chest x-ray showed massive pulmonary oedema. No autopsy was performed. Blood cultures taken during the course of the event were positive for Staphylococcus aureus. The investigator considered that the events were possibly related to the study medication. However, the investigator also considered that the sepsis was related to the localised arm infection and the patient possibly had an allergic reaction to paracetamol.

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ON ORIGINAL



Protocol Id: CNA3008  
Subject number: 11084  
Treatment number:  
Case Id: A0062104  
Trial medication and Dose: Abacavir (Caplet - 300mg)

This 29 year old white female, with a history of cholecystectomy and alcohol abuse, received oral 1592U89 (300mg twice daily) to treat HIV infection. Concurrently, she received oral DMP-266, nelfinavir, and intravenous cefazolin which was replaced with vancomycin for a presumed osteomyelitis of rib fracture. Approximately two weeks after initiating study treatment, she presented to the clinic with overall complaints of feeling ill over several weeks, fever of unknown origin of three weeks duration, anorexia and abdominal pain over a period of one week, increased abdominal girth, and headache. She later presented with nausea and vomiting of one to two months duration as well as headaches, fevers and mental status changes. She was subsequently hospitalized to rule-out lymphoma and/or an abdominal mass. Physical examination on hospital admission revealed a cachectic patient with an elevated temperature, white patches on the tongue, pulmonary bibasilar crackles, and hepatosplenomegaly. Laboratory tests revealed elevated SGPT and total bilirubin and grade 4 levels of SGOT and direct bilirubin which were considered laboratory abnormalities of major clinical concern.

Blood cultures and blood studies for toxoplasma and cryptococcus were negative. Abdominal CAT scan revealed splenic lesions and bone scans revealed lesions in three ribs on the right side and a single rib lesion on the left. The hepatomegaly, persistent fever, and anorexia were considered life threatening and disabling/incapacitating. The grade 4 levels of SGOT and direct bilirubin were also considered disabling/incapacitating. Study drug was discontinued along with all other antiretroviral therapy. The etiology of the hepatomegaly was not identified, although Hepatitis B was considered. In the meantime, the patient was placed on erythromycin for possible Bartonella infection. Due to the rapid decline in her liver function as well as electrolyte abnormalities and unidentifiable cause for her liver disease, she was transferred to a hospice where she later died. Autopsy results revealed pathologic findings of splenic infarcts, metabolic and electrolyte disturbances, and marked hepatomegaly. It appeared that the patient was also hemodynamically compromised near the time of death, possibly secondary to septic shock arising from left lung bronchopneumonia. Multiorgan system failure secondary to shock was seen in various vital organs. Histologic findings revealed acute tubular necrosis, centrilobular liver necrosis, and segmental mucosal necrosis of the small intestines. Inspection of the lungs revealed pulmonary edema and congestion along with diffuse alveolar damage suggesting early adult respiratory distress syndrome. Moderate coronary atherosclerosis and left ventricular hypertrophy were also present, suggestive of systemic hypertension. In the investigator's opinion, the events were related to the use of study drug and to HIV infection.

APPEARS THIS WAY  
ON ORIGINAL

Protocol Id: CNAB3005  
Subject number: 08103  
Treatment number: 00189  
Case Id: B0052544  
Trial medication and Dose: Abacavir/Indinavir, COMBIVIR (Tablet - 1 tablet)

This 42 year old male, naive to anti-retroviral treatment, was receiving oral 1592U89/indinavir and COMBIVIR (lamivudine 150mg + zidovudine 300mg) twice a day for HIV infection. There were no concurrent treatments. There was no history of allergy. Baseline HIV RNA PCR result was 116440 HIV copies/mL. HIV disease status: category A in the CDC classification. On study entry he had nausea, generalised lymphadenopathy and seborrheic dermatitis but no cardiovascular or respiratory problems. On the first day of study treatment, he developed nausea and vomiting. This was followed five days later by fever and diarrhoea. The following day he was seen at the hospital complaining of headaches and persistent nausea. On examination he was pyrexial (>39C), had cervical lymphadenopathy but no oropharyngeal mucosal lesions or rash. A 'flu-like syndrome' was suspected and the patient was given paracetamol and discharged home for bed rest. Next day his fever had increased to >40C, accompanied by persistent nausea, vomiting and worsening diarrhoea and he was admitted to hospital the following day. A rash was noted on admission; the patient indicated that it had appeared one or two days earlier. His blood pressure was low at 83/46. Stool and blood cultures and parasitology tests on the stools were all negative. He was diagnosed with 'infectious diarrhoea' and received IV rehydration and ofloxacin and study medication was interrupted. The fever and diarrhoea subsided by the next day and he was discharged three days after admission complaining still of marked asthenia. Over the following week, the asthenia continued and, in addition, he complained of lower back pain and pain in the right shoulder particularly while in bed at night. Examination of the shoulder revealed no abnormality. At the end of this week he felt very tired and had a persistent mild pyrexia (38 C, most marked in the evening) but he had had no further diarrhoea. ZOVIRAX<sup>†</sup> cream was prescribed for labial herpes. 1592U89 was re-introduced the following day. However, 40 minutes after the ingestion of the first tablet the patient developed severe malaise with a tingling sensation in the lower limbs, a sensation of pressure in the chest, respiratory distress, fever, diarrhoea and syncope. He telephoned his doctor and was advised to discontinue treatment and consult a doctor if symptoms persisted. However, according to a friend, after taking paracetamol, his symptoms improved during the afternoon, though he still had respiratory difficulty, and a doctor was not consulted. During the night he was said to have had a recurrence of the diarrhoea. In the morning he was found dead in his bed by his friend. External examination of the body revealed no obvious cause of death. In particular, there was no evidence of diarrhoea, vomiting or incontinence, no facial asymmetry or other anomaly. No autopsy was performed. The investigator initially considered the gastrointestinal problems and fever to be of viral or infectious origin. Later, the investigator considered the events to be part of a hypersensitivity reaction related to the study medication (1592U89). Subsequently, the investigator stated that 'there is no certainty that the initial episode was due to a hypersensitivity reaction and even less that the death was related to such a reaction. The cause of death is and will stay undetermined'. Other possible causes of death suggested by the investigator, were pulmonary embolism, myocardial infarction or fulminant pneumonia.

Protocol Id: CNA3008  
 Subject number: 10074  
 Treatment number:  
 Case Id: A0058819  
 Trial medication and Dose: Abacavir (Caplet - 300mg)

This 25 year old white female received oral 1592U89, 300mg twice daily, to treat HIV infection. Concurrently she received multiple medications. Approximately ten weeks after initiating study treatment she developed cough, shortness of breath and fever. Five days later she was hospitalized for progressive shortness of breath, cough, fever, nausea and was diagnosed with pneumonia which was considered life threatening and disabling/incapacitating. Upon admission she was found to be severely hypoxic and was intubated. The bronchoscopy, cultures and silver stain were negative. She was noted to have an altered mental status, which prolonged her stay in the intensive care unit for several days. Study drug was interrupted. She was treated with intravenous antibiotics for bacterial pneumonia and with pentamidine and intravenous steroids for possible pneumocystis carinii pneumonia. The events resolved over approximately two weeks and she was discharged home in good condition on oral antibiotics. Study drug was resumed along with the other antiretroviral medications. The day following hospital discharge, she was found dead at home. The cause of death was pneumonia. No autopsy was performed. In the investigator's opinion the events were not related to the use of study drug, and related to the community acquired infection.

Protocol Id: CNA3008  
 Subject number: 10965  
 Treatment number:  
 Case Id: A0061109  
 Trial medication and Dose: Abacavir (Caplet - 300mg)

This 32 year old white male with a history of cerebral atrophy, major depressive disorder with psychotic features and suicide attempts, suicidal ideation, AIDS dementia, wasting syndrome, Pneumocystis carinii pneumonia, hepatitis B, and Clostridium difficile infection received oral 1592U89, 300mg twice daily, to treat HIV infection. Concurrently, he received multiple medications. Approximately three weeks after initiating study treatment, he experienced tenderness and erythema at an old line site, arm pain and sinus congestion. He was noted to be depressed ("down"). He was treated with cephalexin. Four days later, he complained of diarrhea, nausea, sinus problems, insomnia and right arm tenderness near an active line site. Three days later, he complained of insomnia, generalized pain and sinus complaints. Two days later, he complained of diarrhea. Two days later, he did not eat, complained of continued diarrhea and reported a fall the prior evening but denied loss of consciousness. Two days later he continued to have diarrhea, anorexia and emesis. He was tachycardic, pale, and had no palpable blood pressure. He refused hospitalization and remained in his room complaining of not feeling well, nausea, vomiting and weakness. The following day, he was found dead in the bathroom of his room. In the investigator's opinion there were several explanations for the sudden unexpected death which included a possible allergic reaction to the study drug, unexpected interaction between olanzapine and ritonavir, sepsis from the gastrointestinal problem or line infection, and metabolic abnormality that precipitated a cardiac arrhythmia associated with Clostridium difficile diarrhea.

**Protocol Id:** CNAB3001  
**Subject number:** 5004  
**Treatment number:** 54  
**Case Id:** A0055801  
**Trial medication and Dose:** Abacavir (Caplet - 600mg)

This 35 year old male, with a history of Cytomegalovirus retinitis, bacterial pneumonia, deep vein thrombosis of right lower extremity, and seizure disorder (approximately one seizure per year), received oral 1592U89 (600mg twice daily) for HIV infection. Concurrently, he received multiple medications. Approximately one week after initiating study treatment, the patient was hospitalized for fever (104 F.) and headache. Study treatment was interrupted. Blood cultures and chest x-ray were negative on admission. One day prior to admission, a CT with contrast was negative and the patient's mental status remained unchanged from baseline. A gallium scan revealed a 2-3 positive uptake in the lungs for one day, and then resolved. There were no further findings. Three days after admission, the patient experienced two seizures. The following day, he experienced another seizure, followed by cardiopulmonary arrest. The patient was coded for several minutes, and died. No autopsy was performed. In the investigator's opinion, all events were possibly related to the use of the study drug.

**APPEARS THIS WAY  
ON ORIGINAL**

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ON ORIGINAL**

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Protocol Id: CNA3008  
Subject number: 10132  
Treatment number:  
Case Id: A0063560  
Trial medication and Dose: Abacavir (Caplet - 300mg)

This 44 year old black male, with a history of intravenous drug use and hepatitis A, B, and C, received oral 1592U89, 300mg twice daily, to treat HIV infection. Concurrently he received didanosine, fluconazole, hydroxyurea, stavudine, saquinavir, ritonavir and prochlorperazine. Approximately six months after initiating study treatment he experienced intermittent vomiting over an eight-day period. A week later he was noted to be jaundiced and exhibited mental status changes. He presented to the emergency room the next day and was combative and verbally nonresponsive. He was treated with prochlorperazine and doses of fluconazole and didanosine were decreased. He was subsequently hospitalized. Laboratory test revealed Grade four elevations of alanine and aspartate transaminases which were considered laboratory abnormalities of major clinical concern. He was diagnosed with fulminant hepatic failure and study drug and all antiretrovirals were discontinued. Hepatic encephalopathy was thought to explain the patient's mental status changes and concurrent symptoms. He was treated with intravenous fluids, naloxone, amphotericin B, and cefotaxime. While hospitalized he developed coagulopathy and was treated with vitamin K. He later became acidotic and received sodium bicarbonate. Four days following admission, he died due to hepatic failure. No autopsy was performed. The cause of death as stated in the death certificate was fulminant hepatic failure due to a drug reaction and AIDS. A drug interaction between abacavir and prochlorperazine was suspected. In the investigator's opinion, the events were related to the use of study drug. The investigator also considered the patient's history of hepatitis A, B, and C, intravenous drug use, and concurrent antiretroviral regimen (including didanosine, hydroxyurea, stavudine, saquinavir, and ritonavir) to be the other possible causal factors.

Protocol Id: CNA3008  
 Subject number: 11263  
 Treatment number:  
 Case Id: A0068343  
 Trial medication and Dose: Abacavir (Caplet - 300mg)

This 38 year old white male with a history of anemia, fever of unknown origin, aortic stenosis, depression, and intravenous drug abuse received oral 1592U89, 300mg twice daily, to treat HIV infection. Concurrently he received DMP-266. Approximately four months after initiating study treatment he developed severe shortness of breath. He was found dyspneic in his apartment by paramedics and was taken to the emergency room where he was noted to be agitated, febrile, hypotensive, cyanotic, and bradycardic. The patient also noted to paramedics that he was experiencing chest pain. He was rapidly intubated and placed on an external pacer for his bradycardia. On examination, his pupils were dilated and his left eye was deviated inwards. He had loud bilateral rales and rhonchi and inaudible cardiac sounds. He was severely tachypneic. Pulse oximetry was consistent with severe hypoxemia. Electrocardiogram (EKG) revealed right bundle branch block with complete atrioventricular dissociation. Chest X-ray revealed bilateral infiltrates filling both lungs. Laboratory tests revealed elevated white blood cell count, serum glutamic oxaloacetic transaminase and alkaline phosphatase. One of two blood cultures grew coagulase negative staphylococcus aureus which was considered a possible contaminant. Admitting diagnoses included: respiratory failure, rule out community acquired pneumonia, rule out endocarditis with pneumonitis, rule out HIV associated Pneumocystis pneumonia; sepsis, complete heart block, rule out intracoronary abscesses, AIDS; and depression. He was treated with ceftizoxime and midazolam. EKG monitoring revealed sinus rhythm. Two hours later, he developed complete dissociation with third degree heart block. Later that day he was pronounced dead due to respiratory arrest. His hospital stay was approximately six hours. According to the hospital attending physician, "circumstances surrounding the patient's respiratory decompensated condition are not consistent with an identifiable cause of death such as a bacterial pneumonia. Because of this, both study medications and a primary cardiac problem (e.g. aortic stenosis) must be considered as possible causes of death in the context of study evaluation. The patient could have experienced anaphylactic shock leading to congestive heart failure as a plausible cause of death." In the investigator's opinion, the respiratory arrest was related to the use of study drug, staphylococcal infection, treatment failure, and HIV infection.

APPEARS THIS WAY  
 ON ORIGINAL

## **GROUP LEADER MEMORANDUM**

**NDA:** 20-977 (tablets) and 20-978 (solution)

**Drug and Indication:** Ziagen™ (abacavir sulfate) 300 mg tablet and 20 mg/mL oral solution for treatment of HIV-1 infection in combination with other antiretroviral agents

**Dose:** 300 mg twice daily  
8 mg/kg twice daily for ages 3 months to 16 years

**Applicant:** Glaxo Wellcome Inc.

**Submission received:** June 24, 1998

**Date of Memorandum:** December 16, 1998

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The applicant has requested approval for a nucleoside reverse transcriptase inhibitor, Ziagen™ (abacavir sulfate) for the treatment of HIV-1 infection, when used in combination with other antiretroviral agents, under accelerated approval regulations, 21 CFR 314 subpart H. This indication is based on surrogate endpoint analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies up to 24 weeks in duration.

In support of the request for accelerated approval, the applicant has submitted the 16 to 24 week surrogate endpoint data from three controlled clinical trials that enrolled 483 patients. One of these trials, CNA 3006 is being conducted in 205 pediatric patients ages 3 months to 16 years. A second trial CNAB 3001 is being conducted in 105 treatment experienced patients with AIDS dementia. A third, ongoing trial was conducted in 173 treatment-naive HIV-infected adults. The primary efficacy measure was the percent of patients with plasma HIV RNA  $\leq 400$  copies/mL ( $< 10,000$  copies/mL in pediatric study) using approved Amplicor™ Monitor assay. Data from 10 phase I pharmacokinetic and drug interaction studies and six phase II studies were also submitted in support of the application. During the NDA review process, at the division's request the applicant has submitted preliminary data from additional completed and ongoing clinical trials.

A total of 723 patients received abacavir sulfate at various doses across all studies and are included in the safety database. Approximately 578 patients received abacavir at a dose of 300 mg BID for at least 24 weeks. Safety experience was also supported by reported adverse events from phase I/II trials and the expanded access program.

This application was presented to the Antiviral Advisory Committee on November 2, 1998. Seven of nine advisory committee members concluded that the information presented by the applicant supported the safety and effectiveness of abacavir for the treatment of HIV infection under the accelerated approval regulations. Issues raised by Advisory Committee were incorporated into the request for the phase IV commitments and the labeling for abacavir.

I am in agreement with Antiviral Advisory Committee recommendation and the conclusion of the primary medical reviewer that data in this application support the conclusion that abacavir sulfate 300 mg tablets and 20 mg/mL oral solution for use in combination with other antiretroviral agents provides meaningful therapeutic benefit. Therefore, this new drug application should be approved under the accelerated approval regulations. Two 48-week trials evaluating effects of abacavir on long-term suppression of HIV RNA are ongoing and a third one will be initiated in the near future.

The following issues warrant comment at the time of this regulatory action:

### **1. Safety**

The most significant adverse event associated with abacavir therapy is hypersensitivity reaction. Fatal hypersensitivity reaction has been reported with abacavir therapy. In clinical trials, hypersensitivity reaction was reported in approximately 5% of adult and pediatric patients. Signs and symptoms may include, but are not limited to fever, skin rash, fatigue, nausea, vomiting, diarrhea, or abdominal pain. Patients with sign and symptoms of hypersensitivity reaction should discontinue treatment with abacavir immediately. It is of paramount importance that patients with documented hypersensitivity reaction do not restart treatment with abacavir because the recurrent symptoms may be life-threatening or fatal. The description of hypersensitivity reaction was included in the Box Warning section of the labeling for abacavir. Patients will receive Medication guide and Warning card with each new prescription or refill that provide information about hypersensitivity reaction.

Additional adverse events reported with abacavir therapy were nausea, vomiting, diarrhea, headache, and malaise or fatigue. Laboratory adverse events included increase in ALT, creatine phosphokinase, blood glucose and triglyceride levels.

### **2. Description of Clinical Studies and Efficacy Analyses**

Study CNAB 3003 is an ongoing, open-label, randomized trial of abacavir(ABC)/zidovudine(ZDV)/lamivudine(LAM) compared to placebo/zidovudine/lamivudine in 173 HIV-infected treatment-naive adult patients. The study was blinded for the first 16 weeks, when all patients were offered open-label abacavir treatment. This trial provided only 16 weeks of the controlled data.



**Summary of HIV RNA and CD4 - Week 16**

	HIV RNA <400*	Median CD4 change	Discontinuation
ABC/ZDV/LAM	62/87 (71%)	47 cells	13 (15%)
ZDV/LAM	29/86 (34%)	112 cells	18 (21%)

\*includes patients who dropped out of the study and/or did not have a 16 week HIVRNA measured as HIVRNA >400 copies/mL

A significantly higher proportion of patient in the abacavir treatment group had HIV RNA less than 400 copies/mL compared with the ZDV/LAM treatment group at week 16 of study treatment. However, the median CD4 response was lower in the abacavir treatment arm than in the ZDV/LAM. Because of a lower CD4 response in the abacavir treatment group, preliminary 16-24 week surrogate marker data from another ongoing clinical trial were reviewed. This was CNAAB3005, a 48 week, ongoing, equivalence trial, designed to compare abacavir/ZDV/LAM versus indinavir/ZDV/LAM. The preliminary results of this trial supported antiviral efficacy of abacavir in treatment-naive patients.

Study CNAAB 3006 is a 48-week, ongoing, randomized, double-blind, multicenter trial comparing ABC/ZDV/LAM to ZDV/LAM in 205 HIV-infected, treatment-experienced pediatric patients. Patients whose confirmed HIV RNA copy number increase by >0.5 log<sub>10</sub> copies/mL from baseline at week 8 or whose HIV RNA copy number was ≥ 10,000 at week 16 were eligible to receive a) open-label abacavir in combination with ZDV and LAM, b) receive open-label abacavir in combination with any other antiretroviral therapy, or c) continue blinded treatments or withdraw from the trial. Twenty one percent of patients entered the trial with HIV RNA < 10,000 copies/mL.

**Summary of HIV RNA and CD4 cell count**

	ABC/ZDV/LAM	ZDV/LAM
HIV RNA <10,000 copies/mL at week 24	47/102 (46%)	38/103 (37%)
HIVRNA <400 copies/mL at week 24*	12/102 (12%)	1/103 (1%)
Median CD4 change at week 16	69 cells	9 cells

\*Missing data are considered as HIVRNA>400 copies/mL

There was no significant difference between the two treatment arms in the percent of patients achieving plasma RNA levels < 10,000 copies/mL at week 24 of treatment. A significant difference between the abacavir and control treatment groups was seen in the proportion of patients with HIV RNA <400 copies/mL, which was secondary analysis. The low HIV RNA response rate in treatment experienced pediatric population provided evidence of limited efficacy of abacavir in children with prolonged prior treatment with nucleoside analogues.

A third, 12-week, completed clinical trial (CNAB 3001) was conducted in 105 HIV-infected treatment-experienced patients with AIDS dementia. The results of this trial did not demonstrate a significant difference between the abacavir containing and background treatment regimens in surrogate markers response or in neuropsychological performance endpoints. Addition of abacavir to background antiretroviral therapy failed to provide a treatment benefit.

The results of an additional trial (ACTG 368) in treatment-experienced patients did not demonstrate additional antiretroviral treatment effect when abacavir was added to indinavir/efavirenz treatment regimen. Therefore, based on the reviewed data submitted in this application it appears that in patients with a history of prolonged treatment with nucleoside analogues abacavir has a limited antiretroviral treatment effect.

**Proposed Phase IV Commitments**

[Redacted]

abacavir.

/S/

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cc:  
NDA 20-977  
HFD-530/HJolson/TCvetkovich/SKukich