

I. Review Summary

EFFICACY IN INITIAL STUDIES

The original NDA was submitted in June 1998. Three comparative phase three studies and one non-comparative study were included in the initial submission. In the adult naïve study (3003), an HIV-RNA advantage was established relative to placebo. However, a CD4 deficit was also seen which did not appear to be due to chance imbalances. In the pediatric experienced study (3006), while numerical differences favored abacavir, the primary analyses of HIV-RNA and CD4 found no significant advantage (a secondary analysis of <400 copies identified a small but significant difference). In the AIDS dementia study (3001), no significant advantage was seen for AIDS dementia, HIV-RNA, or CD4. There was a suggestion of a CD4 deficit in this study as well. In the expanded access study (3008), only 4% of subjects achieved less than 400 HIV-RNA copies after initiation of abacavir. Thus, the studies submitted with the original NDA did not establish the efficacy of abacavir.

MAJOR CLINICAL AMENDMENTS

To address the concerns regarding efficacy in the original NDA, the applicant submitted preliminary information on four additional studies in October and November of 1998. However, these submissions consisted primarily of executive summaries, and did not include full study reports or complete electronic data. A full FDA review of these studies was not possible due to the late receipt and the incompleteness of the submissions.

PRELIMINARY EFFICACY RESULTS FROM NEW STUDIES

Two of the new studies were analyzed by a third party, the ACTG. In the ACTG experienced study (368), no difference was observed between the abacavir arm and the placebo arm for either HIV-RNA or CD4. In the ACTG equivalence study (372), the confidence bounds for HIV-RNA response were too wide to permit a conclusion of equivalence. The remaining two studies had preliminary analyses performed by the applicant. In 3002, the applicant reported a significant difference relative to placebo for HIV-RNA but not for CD4. In study 3005, the applicant reported that the HIV-RNA results established equivalence to indinavir, and reported that while a possible (study is blinded) numerical CD4 deficit was again seen, the difference was not significant. To reiterate, these claims have not been fully reviewed by FDA. Even granting the results as stated, though, the results from the recent studies showed mixed results.

HYPERSENSITIVITY

The most serious adverse effect of abacavir is the hypersensitivity reaction (HSR). The hypersensitivity reaction has not been well characterized in terms of diagnosis, incidence, time course, and potential predictors. The characterization of the reaction has been hampered by discrepancies between the case report forms and the SAE reports filed directly with the applicant. The applicant has reported that the incidence of HSR is approximately 3%. Based on preliminary FDA review of the two largest studies (3005, 3008), it appears that the incidence may be as high as 7-8%.

CONCLUSION

The studies submitted with the original NDA did not clearly establish the efficacy of abacavir. The efficacy concerns are heightened by the fact that abacavir causes a serious hypersensitivity reaction, and this reaction is not well understood. The recent studies showed mixed results from preliminary data that was not reviewed fully by FDA. The recent results therefore do not overcome the lack of convincingly demonstrated efficacy in the original submission.

II. Efficacy

Three Phase III studies were submitted for accelerated approval with the original NDA in June of 1998. Of these, two studies were designed as principal efficacy studies for the HIV indication: study 3003 and study 3006. Study 3003 was a study in treatment-naïve adults, with 16 weeks of comparative RNA and CD4 data. Study 3006 was a study in treatment-experienced children, with 24 weeks of comparative RNA and CD4 data. This review will focus on the results of these two principal studies. Two additional studies provide some supportive efficacy data. Study 3001 was designed to test the effect of abacavir on AIDS dementia, with 12 weeks of comparative RNA and CD4 data. Study 3008 was an expanded access safety study with a single arm and 8 weeks of RNA and CD4 data.

The initial review of the studies submitted in the NDA raised serious questions about the approvability of the application. To address these concerns, the applicant submitted preliminary results from four additional studies in October and November of 1998. However, these submissions consisted primarily of executive summaries, and did not include full study reports or complete electronic data (see Table 1). The FDA review summarizes the results as reported in the executive summaries and provides comments on these results. However, a full independent review of these studies was not possible due to the timing and incompleteness of the submissions.

Table 1: Submissions as of 11/98 (see Appendix for Timeline)

	Principal Efficacy		Supportive Efficacy		Recent Efficacy Data			
	3003	3006	3001	3008	3005	368	372	3002
Study Report	yes	yes	yes	yes	no	ACTG ¹ report	ACTG ¹ report	yes
Results Complete	yes	missing 24 week CD4	yes	yes	missing 24 week RNA, CD4	yes	yes	yes
Electronic Dataset	yes	yes	no	yes	incomplete ²	no	no	yes

¹ACTG statistical summary ²Does not include demographics, center, and other key variables

The review will focus on the results of the two principal studies 3003 and 3006. However, the other studies provide additional important information. Section 1 summarizes the designs and demographic characteristics of the eight studies. Sections 2-4 discuss the results from the principal, supportive, and recent studies respectively. Finally, section 5 summarizes the key efficacy results for all of the studies.

1. Study Designs

Table 2: Study Designs

	Principal Efficacy		Supportive Efficacy		Recent Efficacy Data			
	3003	3006	3001	3008	3005	368	372	3002
Pop.	Adult	Ped.	Adult	Adult	Adult	Adult	Adult	Adult
Trt. Exp.	Naïve	Exp	Exp	Exp	Naïve	Exp	Exp	Exp
Endpoint	RNA	RNA	Dementia	Safety	RNA	RNA	RNA	RNA
Duration	16 wks	24 wks	12 wks	8 ¹ wks	24wks	16 wks	16 wks	16 wks
RNA ²	Any	Any	Any	>30,000	>10,000	any	≥500	<50,000
CD4 ²	≥100	Any	Any	<100	≥100	Any	Any	≥100
Design	Placebo	Placebo	Placebo	1 arm	Equiv	Placebo	Equiv	Placebo
ABC arm ³	A/Z/3	A/Z/3	A/Back	A/Any	A/Z/3	A/I/E	A/D/E	A/Back
Control ³	Z/3 -	Z/3	Back	—	I/Z/3	I/E	Nu/D/E	Back
N/arm	87/86	102/103	52/53	200	280/282	140/143	50/44	92/93
Primary analysis	% RNA <400	% RNA <10,000	Neuro-psych	Safety	% RNA <400	% RNA <500	% RNA <500	% RNA <400
Secondary analyses	CD4	<400, CD4	RNA, CD4	RNA, CD4	CD4	CD4	CD4, CD8	CD4

¹Efficacy substudy ²Entry Criteria ³A=abacavir, Z=Zidovudine, 3=3TC, I=indinavir, E=efavirenz, N=nelfinavir, D=adefovir, Nu=nucleosides, back=background therapy, any= any other regimen

Table 3: Study Demographics and Baseline Characteristics

	Principal Efficacy		Supportive Efficacy		Recent Efficacy Data			
	3003	3006	3001	3008	3005	368	372	3002
N/arm	87/86	102/103	52/53	200	280/282	140/143	50/44	92/93
Gender ¹	82M/18F	44M/56F	98M/2F	94M/6F		79M/21F	73M/27F	79M/21F
Race ²	54W/28B	17W/50B	81W/12B	81W/9B		37W/41B	41W/38B	91W/5B
Age ³	34	6	41	41		40	39	37
RNA ³	39,000	39,500	12,600	246,000	72,400	20,000	39,100	4,100
CD4 ³	443	690	170	24	357	135	196	409
ART ⁴	Naïve	Exp	Exp	Exp	Naïve	Exp	Exp	Exp
ZDV	—	80%	56%	90%	—	100%	100%	66%
3TC	—	55%	81%	79%	—	100%	100%	71%
NNRTI	—	1%	>9%	47%	—	0%	0%	2%
Protease	—	6%	>38%	97%	—	0%	100%	20%

¹Percent Male/Female ²Percent White/Black (remainder predominantly Hispanic) ³Median ⁴Prior anti-retroviral therapy (naïve/experienced), and percent of subjects with experience to each listed therapy

2. Study Results (Principal Efficacy)

This section discusses the individual study results for the two principal clinical trials.

2.1 ADULT NAÏVE (STUDY 3003)

Study 3003 was conducted in treatment-naïve adults. Subjects were randomized to either ABC+ZDV+3TC or ZDV+3TC. Subjects were stratified by baseline RNA (<10,000 / 10,000-100,000 / >100,000). The first 16 weeks of the study was the comparative phase; after 16 weeks subjects on both arms could receive open label abacavir or switch to another regimen. This switch could occur regardless of whether subjects were being successfully suppressed to below 400 copies. The majority of subjects on both arms switched to open label ABC+ZDV+3TC after 16 weeks. Therefore, the review will focus on the 16 week results as the most meaningful for assessing relative efficacy.

Table 4 summarizes the disposition of subjects at week 16. The dropout rate was 7% (12/173), and an additional 5% (8/173) of subjects were still being followed on study past 16 weeks but missed their week 16 visit.

Table 4: Study 3003 Subject Disposition

	ABC+ZDV+3TC	ZDV+3TC
Randomized	87	86
Data at Week 16	74	68
No Data at Week 16	13	18
No Study Drug	4	5
Dropout	5	7
Missed Week 16	4	6
On Treatment at Week 16	75	73

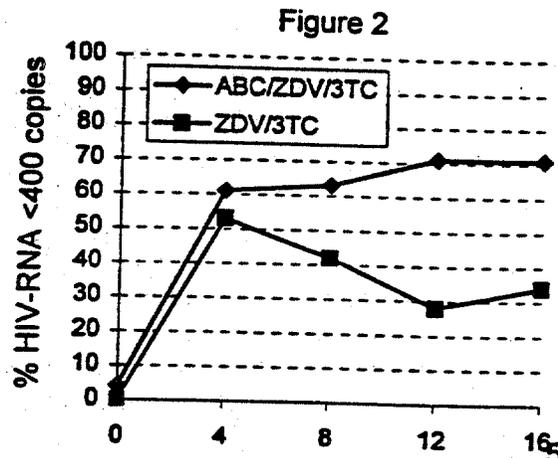
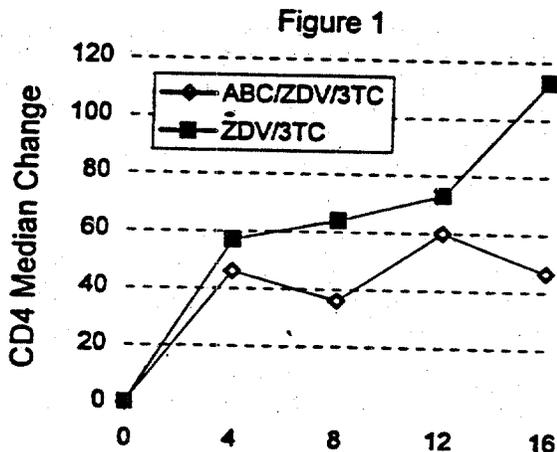
HIV-RNA AND CD4 RESULTS

The results at week 16 are summarized in Table 5 and Figures 1 and 2. The percent of patients less than 400 copies at 16 weeks was significantly greater in the abacavir arm. Missing data was considered to be above 400 copies in this analysis. The CD4 response was less in the abacavir arm compared to the control arm for subjects with data at 16 weeks.

Table 5: Study 3003 Week 16 Results

	ABC+ZDV+3TC	ZDV+3TC	Difference
Known <400 copies	62/87 (71%)	29/86 (34%)	37% (p=.001 ¹)
Median change in CD4	46.5 cells (n=74)	113 cells (n=68)	-67 cells (p=.089 ²)

¹Fishers Exact Test (FDA analysis) ²Stratified Wilcoxon (FDA analysis)



The CD4 response not only was lower on the abacavir arm, but a greater number of subjects on the abacavir arm had CD4 counts that declined to below their baseline level (Table 6).

Table 6: Study 3003 CD4 Results

	ABC/ZDV/3TC	ZDV/3TC
CD4 Decrease from Baseline	25/81 (31%)	16/78 (21%)

Comparative CD4 results post-week 16 are not interpretable since the majority of subjects switched to open label triple therapy.

INCONSISTENCY OF HIV-RNA AND CD4

The lack of agreement between the treatment effects relative to control for the two markers HIV-RNA and CD4 is disturbing. The model of treatment induced marker changes suggests that the anti-viral activity of the drug reduces the number of viral copies, which results in an improvement in the subject's immune system, which will then result in a lower rate of infections and death. This implies that the anti-viral advantage over control should have translated into a corresponding improvement over control in immune function as measured by CD4 cell count. In recent applications, RNA differences versus control have been seen in conjunction with either significant CD4 advantages or non-significant CD4 advantages. In this study, not only was there no such CD4 advantage, there was a striking deficit. The magnitude of the deficit is comparable to the magnitude of CD4 differences that have been used as the basis for accelerated approval when CD4 was the primary endpoint of HIV trials.

SURROGATE MARKER EFFECTS

Another area of concern lies in the calculation of the overall net benefit of abacavir in the study. Both HIV-RNA and CD4 are surrogate markers, meaning that changes in these markers predict subsequent changes in clinical event rates. If we consider CD4 on its own, then the abacavir arm would have a higher predicted clinical event rate than the control arm. Conversely, if RNA were considered on its own, the abacavir arm would have a lower predicted clinical event rate. This implies that we need to consider both markers simultaneously.

The ACTG recently published the results of an analysis correlating RNA and CD4 changes with subsequent clinical event rates. The ACTG analysis included only patients on nucleoside-based therapy. They found that a 50 cell increase in CD4 cell count was associated with a clinical event rate reduction of about 23%, and a .5 log decrease in viral load was associated with about a 22% clinical event rate reduction.

Table 7: Study 3003 Surrogate Marker Prediction of Clinical Effect

	CD4			HIV-RNA			Combined Risk Red.
	Increase	Inc/50cell	Risk Red.	Decrease	Dec/.5log	Risk Red.	
ABC	46.5	0.93	21%	1.75	3.5	58%	67%
Control	113	2.26	45%	1.17	2.3	44%	69%

Since the RNA assay has a lower limit of 400 copies, subjects who reached this limit may have had a greater decrease from baseline than was calculated. This means that the HIV-RNA decreases in the table may be underestimates. A supplemental analysis gave subjects who reached 2.6 log copies (400 copies) an additional .5 log reduction down to 2.1 log copies (125 copies). In this analysis, the ABC arm was associated with an estimated combined risk reduction of 70%, using the ACTG estimated model

parameters, and the placebo arm was also associated with an estimated combined risk reduction of 70%. Again, there was no evidence for an advantage of ABC over placebo in terms of projected clinical event rates. There are caveats to the specific numbers in this analysis (for example the ACTG analysis population was more advanced than the study 3003 population). However, the bottom line is that it is not clear whether a clinical advantage can be anticipated for abacavir compared to placebo.

FURTHER ANALYSIS OF CD4 FINDINGS

Clearly, if the CD4 deficit relative to control is real then there are serious consequences for the assessment of the efficacy of abacavir. Therefore, several avenues were identified for further investigation of the CD4 findings.

FDA conducted analyses to rule out possible alternative explanations, such as baseline imbalances or the possibility that a particular subset of patients might be driving the results. Table 8 summarizes the subgroup analyses. A consistent CD4 deficit relative to placebo was seen in these analyses.

Table 8: Study 3003 Subgroup Analysis of Median CD4 Change at Week 16:

Analysis	Strata	ABC/ZDV/3TC	ZDV/3TC	Difference
All Subjects		47	113	-67
Baseline HIV-RNA	<10,000	23	84	-62
	10-100,000	53	117	-65
	>100,000	73	124	-52
Baseline CD4	<450 ¹	58	113	-55
	>450	31	116	-85
Gender	Male	46	110	-64
	Female	57	122	-65
Race	White	58	121	-63
	Non-white	23	84	-61

¹Median baseline CD4, other cutpoints yielded similar results

As Table 9 illustrates, the CD4 deficit relative to placebo was matched by significant deficits in the non-CD4 component of lymphocytes as well as the total lymphocyte count.

Table 9: Study 3003 Median Change in Lymphocytes at Week 16

	ABC/ZDV/3TC	ZDV/3TC	Difference ¹
Total lymphocytes	-25	154	-180 (p=.01)
CD4 Lymphocytes	47	113	-67 (p=.089)
Non-CD4 lymphocytes	-113	44	-157 (p=.008)

¹Stratified Wilcoxon (FDA analysis)

A total of 22 subjects had CD4 data post baseline but did not have a week 16 value, either because the subjects dropped out or simply missed the week 16 visit. Table 10 shows the median of the last recorded CD4 values prior to week 16 for these subjects. The subjects who did not have a week 16 CD4 value were clearly different than those who had, with CD4 changes approximately 70 cells less than those with complete data. This is not surprising, since study discontinuation is commonly related to lack of efficacy in HIV trials. However, the difference between the two arms for the dropouts is of the same magnitude as for those with complete data. Thus, the presence of missing data is unlikely to have produced a bias in the treatment comparison.

Table 10: Study 3003 Effect of Missing Data on CD4 Results

	ABC/ZDV/3TC	ZDV/3TC	Difference
Observed Data: Week 16	47 (n=74)	113 (n=68)	-67
Missing Data: Last prior to week 16	-19 (n=9)	46 (n=13)	-65
Combined Data	45 (n=83)	100 (n=81)	-55

CONTROL ARM RESPONSE IN OTHER STUDIES

To address the question of whether CD4 response for the control arm might be unusually high, we looked for studies with similar designs (New Drug/ZDV/3TC versus ZDV/3TC in treatment naïve adults) in other applications. Two studies met these criteria. Study Dupont005 (NDA 20-972) compared EFV/ZDV/3TC versus ZDV/3TC, and Study Agouron511 (NDA 20-799) compared NFV/ZDV/3TC to ZDV/3TC. Results for these studies are summarized in Table 11.

Table 11: Results From Similar Studies (Week 16)

	% RNA <400 copies		CD4 Change	
	Triple	ZDV/3TC	Triple	ZDV/3TC
Dupont 005	76%	36%	120	102
Agouron 511	73%	30%	130	90
GW 3003	71%	34%	47	113

The HIV-RNA responses in both the new drug arms and the control arms were similar to those seen in Study 3003. But unlike Study 3003, the triple therapy arms had superior CD4 responses to the ZDV/3TC arms. The CD4 response for ZDV/3TC in Study 3003 is consistent with the CD4 response from these two studies. However, the CD4 response for ABC/ZDV/3TC in Study 3003 was not only lower than the triple therapy arms, but was lower than the control arms as well.

NEW CD4 DATA

In December of 1998, the applicant provided the results of the third arm of study 3003. This arm received open-label triple therapy, and was enrolled after the randomized portion of the study had finished enrolling. This arm was not intended to be part of the primary analysis of this study, however, these subjects do provide potentially useful supplemental data for the ABC/ZDV/3TC arm since they were enrolled in the same study and were on the same treatment regimen. Fifty-eight subjects were enrolled into this arm. At sixteen weeks, 64% of subjects were less than 400 HIV-RNA copies. The median CD4 response at week 16 was 71 cells. This is again lower than the CD4 response in the placebo arm (71 cells – 113 cells = -42 cells). The median CD4 response for both triple therapy arms combined was 57 cells, 56 cells lower than placebo response of 113 cells. The results from this arm are consistent with a CD4 deficit for abacavir relative to placebo.

CONCLUSION

A significant effect on HIV-RNA was seen in this study. However, a CD4 deficit was also seen. The CD4 analyses indicate that the overall CD4 results are not due to chance imbalances, and recent data seem to provide further evidence for a CD4 deficit. The combined effect on HIV-RNA and CD4 do not demonstrate a clear benefit for abacavir. The Guidance for Providing Clinical Evidence of Effectiveness bears directly on this study: "...inadequacies and inconsistencies in the data, such as lack of expected other effects accompanying the critical outcome, can weaken the persuasiveness of a single trial."

2.2 PEDIATRIC EXPERIENCED (STUDY 3006)

Study 3006 compared the same treatment arms as study 3003, ABC+ZDV+3TC vs. ZDV+3TC, but in a population of treatment experienced children. Stratification was by age (<30 months / >30 months) and prior treatment with both ZDV and 3TC in the previous 6 months (both ZDV and 3TC / one or neither of ZDV and 3TC). Full week 24 follow-up was available for HIV-RNA, although full CD4 follow-up was only available through week 16 (the lab used for CD4 for some subjects had not reported the data to the applicant). The median duration of prior ZDV use was 12 months, and the median duration of prior 3TC use was 3 months.

Subject disposition at week 24 is summarized in Table 12. Overall, 12% of subjects dropped out in the first 24 weeks of the study.

Table 12: Study 3006 Subject Disposition

	ABC+ZDV+3TC	ZDV+3TC
Randomized	102	103
Data at Week 24	86	89
No Data at Week 24	16	14
No Study Drug	0	0
Dropout	14	10
Missed 24	2	4
On Treatment at Week 24	86	90

HIV-RNA AND CD4 RESULTS

Results for study 3006 are summarized in Table 13 and Figures 3 and 4. No significant difference was seen in the protocol-specified primary endpoint, HIV-RNA <10,000 copies. CD4 responses were not significantly different between abacavir and placebo, though responses were numerically greater on the abacavir arm. A secondary analysis of the proportion below 400 HIV-RNA copies was statistically significant.

Table 13: Study 3006 Results

	ABC+ZDV+3TC	ZDV+3TC	Difference
Known <10,000 copies (Week 24)	47/102 (46%)	38/103 (37%)	9% (p=.20 ¹)
Median CD4 Change (Week 16 AUCMB)	51 cells	30 cells	21 (p=.074 ²)
Known <400 copies (Week 24)	12/102 (12%)	1/103 (1%)	11% (p=.001 ¹)

¹Fishers Exact Test (FDA analysis) ²CMH Test (GW analysis)

Figure 3

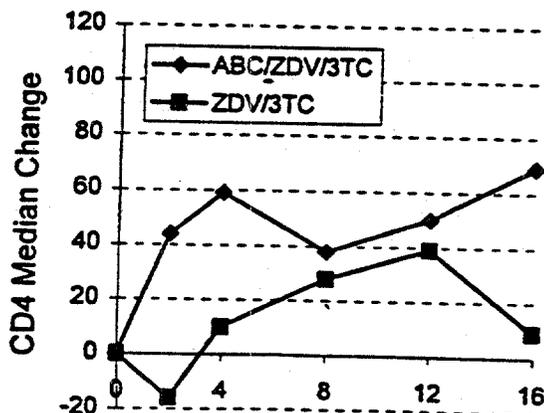
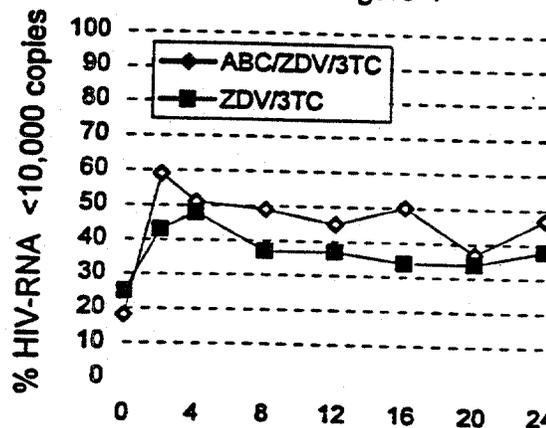


Figure 4



EFFECT OF PRIOR THERAPY

Exploratory analyses were conducted to examine the effect of type and duration of prior therapy on HIV-RNA response. Subjects with prior 3TC received no anti-viral benefit from abacavir (43% <10,000 for abacavir, 48% <10,000 for control, difference -5%), while subjects without prior 3TC had a greater response to abacavir (50% <10,000 for abacavir, 23% <10,000 for control, difference 27%). Duration of prior 3TC use was not found to be an important predictor of response. That is, there did not seem to be any particular level of 3TC exposure below which a response to abacavir might be anticipated (other than having no 3TC experience at all). Analyses of other anti-retroviral therapies did not identify any significant effects of prior treatment.

RESPONSE RATES

The primary analysis of HIV-RNA and the analysis of CD4 changes did not establish a significant difference between abacavir and placebo. At 24 weeks, 46% of subjects on the abacavir arm had reached less than 10,000 copies and 12% had reached less than 400 copies. These response rates should be interpreted in the context of the HIV-RNA at baseline. The median HIV-RNA was 39,500 copies, similar to that in the adult 3003 study. And 20% of subjects started the study already below 10,000 copies. Of the 12 subjects on abacavir who were below 400 copies, 5 had baseline HIV-RNA values less than 1,000 copies and 9 had baseline HIV-RNA values less than 10,000 copies. In this context, the response rates for both analyses were quite low. In this patient population with relatively low levels of virus at baseline, achieving a value of 10,000 copies or even 400 copies should not be difficult.

The response rate peaked at week 2 and steadily declined after that. The small, transitory treatment effect seen in this study may not be predictive of an eventual clinical benefit for abacavir.

The low response rates stand in contrast with the recent ACTG 382 study (see Medical Review of NDA 20-972), which looked at HIV-RNA response in the pediatric population. The study population was very similar to the population in study 3006. The median age was 7 years and subjects had extensive treatment experience. A total of 57 subjects received the combination efavirenz and nelfinavir (no control arm). At 12 weeks, 67% of subjects were less than 400 copies; at 20 weeks 50% of subjects were less than 400 copies. While the study did not have a control arm, the results showed that a substantial proportion of patients can be suppressed to below 400 copies in the treatment experienced pediatric population.

CONCLUSION

In summary, the results of this study (no significant difference for HIV-RNA or CD4 in the primary analysis, low HIV-RNA response rates) provide only limited evidence for the efficacy of abacavir.

3. Study Results (Supportive Efficacy)

This section summarizes the efficacy results for studies 3001 and 3008.

3.1 AIDS DEMENTIA (STUDY 3001)

Subjects in study 3001 were randomized to add either abacavir or placebo to other anti-retroviral therapy for 12 weeks. This study was designed to test the effect of abacavir on AIDS dementia, with RNA and CD4 as secondary endpoints. Subjects were required to have been on their current anti-retroviral therapy (ART) regimen for at least 8 weeks, with stratification by current ZDV use (yes/no).

Subject disposition is summarized in Table 14. The dropout rate over 12 weeks was 15%.

Table 14: Study 3001 Subject Disposition

	ABC+Background	Background
Randomized	52	53
Data at 12 Weeks	37	39
No Data at 12 Weeks	15	14
No Study Drug	3	3
Dropout	7	9
Missed 12	5	2
On Treatment at Week 12	42	41

EFFICACY RESULTS

Table 15 summarizes the efficacy results. The primary endpoint was the change in the neuro-psychologic score over 12 weeks. For this endpoint, no advantage was seen for the abacavir arm over placebo. In addition, no advantage was seen in the protocol-specified analyses of HIV-RNA or CD4. There was a numerical CD4 deficit for the abacavir arm relative to placebo.

Table 15: Study 3001 Week 12 Results

	ABC+ Background	Background	Difference
Change in NeuroPsych Score	.76	.63	.13 (p=.735 ¹)
RNA Change AUCMB	-.04	0	-.04 log (p=NR ²)
RNA Observed Change	-.01	-.09	.08 log (p=NR)
CD4 Change AUCMB	-1	49	-50 cells (p=NR)
CD4 Observed Change	9	-1	10 cells (p=NR)

¹Stratified Wilcoxon (GW analysis) ²NR = not reported

CONCLUSION

In summary, the results of this study (no significant difference for AIDS dementia, HIV-RNA or CD4) provide no evidence for the efficacy of abacavir.

3.2 EXPANDED ACCESS (STUDY 3008: EFFICACY SUBSET)

Subjects enrolled in this open-label, uncontrolled study received abacavir plus at least one new ART to which the subject had not been previously exposed. The first 200 patients enrolled in 3008 were entered in the efficacy substudy, and had HIV-RNA and CD4 assessments for at least 8 weeks. These subjects were treatment experienced and were more advanced than subjects from the other studies.

Subject disposition is summarized in Table 16.

Table 16: Study 3008 Subject Disposition

	ABC+Any
Randomized	200
Data at 8 Weeks	163
No Data at 8 Weeks	37
No study Drug	8
Dropout	
Missed Week 8	29 ¹
On Treatment at Week 8	Not reported

¹Dropouts and missing data not distinguishable with current data

EFFICACY RESULTS

Study results are summarized in Table 17. The median change in RNA (-.19 log copies) was within the range of assay variability (~.5 log). The applicant did not report the CD4 results. Only 8 subjects (4%) had RNA <400 copies after 8 weeks. The majority of subjects initiated abacavir therapy with 2 additional new anti-retroviral drugs. It is not possible to determine what portion of the -.19 log change may be due to abacavir and what may be due to the other drugs.

Table 17: Study 3008 Results

	ABC+Any
RNA Change from Baseline	-.19 log copies
Change >.5log	41 (21%)
Change >1log	16 (8%)
<400 Copies	8 (4%)
CD4 Change from Baseline	Not reported

CONCLUSION

The median change in RNA (-.19 log copies) was within the range of assay variability (~.5 log). The results from this study, while uncontrolled, indicate that the impact of abacavir therapy in more advanced patients may be minimal.

5. Efficacy Summary

Table 26: Summary of Efficacy

Study	Full FDA Review	Control	Primary RNA Analysis	HIV-RNA Effect ¹	CD4 Effect	Notes
3003	Yes	Placebo	% RNA <400 wk 16	37%*	-67	-Surrogate marker model shows no net benefit CD4 deficit w/recent data
3006	Yes	Placebo	% RNA <10,000 wk 24	9%	+21	-Only 12% <400 HIV-RNA copies
3001	Yes	Placebo	Δ RNA wk 12	-.04 log ³	-50	-Also no difference in dementia analysis
3008	Yes	—	Δ RNA wk 8	-.19 log ⁴	NR	-Only 4% <400 HIV-RNA copies
3005	GW only	Active	% RNA <400 wk 16	-3% ⁵	-20 ⁵	-16 weeks too early to assess equiv. -High dropout rate
368	ACTG only	Placebo	% RNA <500 wk 16	2%	-1	-Largest placebo controlled study
372	ACTG only	Active	% RNA <500 wk 16	2%	-1	-CI too wide for equiv. -ABC: more early failures -CD8 deficit
3002	GW only	placebo	% RNA <400 wk 16	29%*	+22	-No effect in subjects > 5,000 copies at baseline

*Significant difference ¹Proportion success for abacavir arm – proportion success for control arm ²Change in CD4 for abacavir arm – change in CD4 for control arm ³Change in HIV-RNA for abacavir arm – change in HIV-RNA for control arm ⁴Change in HIV-RNA for abacavir arm (uncontrolled) ⁵Study blinded, difference assuming abacavir is arm A

PLACEBO-CONTROLLED STUDIES

Three of the five placebo-controlled studies did not show a significant difference between abacavir and placebo. One of the studies that did show an anti-viral advantage (3003) also showed a CD4 deficit that may effectively cancel the anti-viral benefit. The remaining study (3002) has not undergone an independent FDA review.

EQUIVALENCE STUDIES

The two equivalence studies had early data (16 weeks) with confidence intervals outside the range generally considered for similarity. Study 372 is not likely to support equivalence. Study 3005 needs more follow-up (through 48 weeks) and a full FDA review before conclusions can be drawn.

CD4 DEFICIT

While the largest and most robust CD4 deficit was seen in study 3003, study 3001 also suggests an adverse impact of abacavir on CD4 cell count relative to control. Study 3005, which is still blinded, did not rule out the possibility of a CD4 deficit. Study 3003 also showed more subjects whose CD4 dropped to below baseline. The recent data from the open-label abacavir arm in study 3003 showed a similar deficit. The only study (372) that reported CD8 results showed a deficit for abacavir.

ANTI-VIRAL ACTIVITY IN TREATMENT EXPERIENCED SUBJECTS

While a significant HIV-RNA difference was seen in Study 3002, the results of five studies: 3006, 3001, 3008, 368, 372 showed little evidence of efficacy in treatment experienced subjects. Given that there is a significant safety concern associated with

abacavir, the consistently limited efficacy shown for abacavir would appear to preclude its use in treatment experienced patients.

III. Safety

This section will address the primary safety concern about abacavir: the hypersensitivity reaction. For a more extensive review of safety, refer to the Medical review.

1. Data Sources

An understanding of the various safety data sources is critical when interpreting the abacavir safety findings. There were two primary ways in which safety data were captured. The first is through the case report forms. These data were then converted into an electronic database; this will be referred to as the CRF database. The second mechanism is via serious adverse event reports, reported directly to the company. These will be referred to as the SAE reports. Due to the speed of their processing, the SAE reports can be expected to include events that have not yet made it into the electronic CRF database.

A preliminary review of these two sets of safety data found significant discrepancies between the two. These discrepancies were not explained by the time lag in the CRF database, since discrepancies were seen for patients whose CRFs had been completely incorporated into the CRF database. Adverse events reported through the SAE system were not always recorded in the CRFs, and serious events in the CRFs were not always reported through the SAE system. At the time of this review, these discrepancies have not been resolved.

In addition, the criteria used to determine whether a set of adverse events did or did not constitute a HSR are variable. Subjects did not always have a specific diagnosis of abacavir HSR, so that determination of HSR was based on whether their recorded adverse event profile met certain case definitions. The applicant excluded some reactions based on the subject having other underlying conditions that may have produced an HSR-like response. Conversely, some subjects were classified by the investigator as having had an HSR with no other adverse event information recorded.

2. Incidence

The CRF database flags subjects with abacavir HSR reactions. The SAE reports are in the form of patient narratives. The medical reviewer reviewed these reports and flagged subjects with known or probable HSR. Table 27 lists the number of cases from the CRF database and the number of extra reactions identified through the SAE reports. Hypersensitivity information has not been reported for the two ACTG studies (338, 372). For the more recent studies (3002, 3005), the SAE reports have not yet been reviewed.

Table 27: Incidence of Hypersensitivity

Study	Subjects on abacavir	HSR Cases		Total	
		CRF Database	Additional HSR in SAE Reports	Number of Cases	Incidence
2001	78	3	0	3	4%
2002	60	2	1	3	5%
2003	32	0	0	0	0%
2004	74	4	0	4	5%
3001	49	1	2	3	6%
3003	83	2	2	4	5%
3006	102	4	0	4	4%
ACTG 372	50	NA ¹	NA ²	NA	NA
ACTG 368	-140	NA ¹	NA ²	NA	NA
3002	91	3	NA ²	3	>3% ³
3005	263	13	NA ²	13	>5% ³
3008	2409 ⁴	115	42	157	7%

¹CRF data not available ²SAE reports not available ³Incidence not counting HSR from SAE reports
⁴Includes subjects with at least 6 weeks of data through July, 1998

The largest randomized clinical trial, Study 3005, suggests that that rate of HSR is at least 5%, since the SAE reported hypersensitivity reactions have not yet been counted. Based upon the phase III studies in the NDA (3001, 3003, 3006), it appears that the CRF database typically captured about two-thirds of the reactions. Thus a rate of 7-8% is a reasonable estimate for the rate of HSR in Study 3005. This rate of 7-8% is similar to the rate in the expanded access study (3008), where the rate was 7%.

The problems with the inconsistent reporting of the reaction and the uncertainties regarding what was actually called an HSR, outlined above, have an unknown impact on these estimated incidence rates.

It appears that in the most recent studies (adult equivalence 3005, expanded access 3008) the rate of HSR is higher (7-8%), than in the earlier phase II and II studies (3-6%). This may be due to increasing recognition and reporting of the reaction.

3. Predictors of Hypersensitivity

Analyses to determine potential risk factors should be viewed as preliminary due to the uncertainties regarding the safety database outlined above. Since most of the hypersensitivity reactions came from Study 3008, analyses were restricted to those subjects (2409 subjects, 157 with HSR).

The risk was somewhat higher for subjects with higher baseline viral loads (relative risk increase of 20% for each 1 log increase in baseline HIV-RNA, p=.20 from logistic regression analysis). The risk was somewhat higher in females compared to males (9% versus 6%, p=.16). The risk was higher in subjects less than 30 years of age (10% versus 6%, p=.05). The risk was somewhat higher in subjects with greater than one year of nevirapine experience (11% versus 6%, p=.16).

The SAE reports did not typically contain the date of onset of the hypersensitivity reaction. Therefore, analyses to characterize the time of onset of HSR cannot be performed. In addition, analyses to determine potential predictors of onset time (early versus late onset, for example) cannot be done at this time.

4. Unanswered Questions

There are several unanswered or partially answered questions regarding the hypersensitivity reaction. The most important is to resolve the issues plaguing the safety database. Without a resolution of the problems the analyses based on the current information are suspect. Even basic information, such as which subjects had a reaction, how was it diagnosed, and what was the time of onset, is missing in many cases. The following is a list of questions that need to be addressed.

Who actually had an HSR? Why was it reported in some cases on the CRF and in some cases via a SAE report, and why is the information in the two sets of data inconsistent? How was it diagnosed (for some patients the reports just indicate "HSR" with no other information)? Many subjects did not have an explicit HSR yet seemed to have had the reaction: what about other case definitions of HSR that might yield a different incidence? What would a more comprehensive analysis of predictors find? When did the reaction occur (we do not have the time of onset for many patients)? How long did it take from onset of symptoms until diagnosis? How long did symptoms take to resolve? Are there any predictors of time of onset? Since HSR can manifest as fairly common signs (including fever, nausea, tiredness, or rash), what is the incidence of HSR-like symptoms that are not HSR?

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IV. Conclusion

Efficacy was not clearly established with the original studies. Major amendments (both efficacy and safety) were submitted in the final weeks of the review. The efficacy results from these studies showed mixed results. However, the recently submitted studies were not fully reviewed by FDA.

Abacavir causes a serious and unpredictable hypersensitivity. Much is not known about this reaction. The hypersensitivity reaction has not been well characterized in terms of diagnosis (how can it be distinguished from other common adverse events), incidence, time course, and potential predictors. Additionally, there are serious discrepancies in the safety database.

In treatment naïve subjects, abacavir appears to have anti-viral activity with respect to HIV-RNA, but possibly a negative immunologic effect in terms of CD4. Since both HIV-RNA and CD4 are surrogate markers, any assessment of clinical benefit must take both marker effects into account. When the risk for hypersensitivity and the potential for cross-resistance are added, the risk benefit ratio does not appear to support abacavir, particularly since naive patients have many other treatment options.

In treatment experienced patients the risk/benefit ratio is even clearer, as there are five studies that suggest abacavir is at best minimally effective.

From the perspective of this review, the approval of abacavir for the treatment of HIV infection has not been adequately supported at this time.

/S/

Michael Elashoff, PhD
Division of Biostatistics
December 16, 1998

Concur: Paul Flyer, PhD.

/S/

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V. Appendix

Table 28: Timeline of Submissions Containing New Data

Date	Content
06/24/98	NDA submitted
06/24/98	16 week efficacy data for Studies 3003, 3006
08/07/98	Safety Update
08/07/98	Safety data for Study 3001, 3003, 3006
08/07/98	Efficacy data for Study 3008 (efficacy substudy)
08/07/98	24 week efficacy data for Studies 3003,3006
10/02/98	ACTG statistical report for Study 372
10/02/98	Safety data for Study 3008 (data through June 1998)
10/09/98	ACTG statistical report for Study 368
10/09/98	Additional efficacy data for 3006, 3008
10/13/98	Efficacy data for Study 3005 (dataset is missing key variables, some patients without 16 weeks follow-up)
10/16/98	Study Report for Study 3002
10/16/98	Efficacy and Safety data for Study 3002
11/02/98	Advisory Committee Meeting
11/09/98	Merged Safety Database (data only through March 1998)
11/13/98	Safety, Lab data for Study 3005
11/13/98	Updated efficacy data for Study 3005 (all patients through 16 weeks, but still missing key variables)
12/01/98	RNA, CD4 Data for Study 3003 (ABC/ZDV/3TC open label arm)

VI. Distribution List

cc:

Archival NDA# 20,972
HFD-530/Ms. Truffa
HFD-530/Dr. Cvetkovich
HFD-530/Dr. Kukich
HFD-530/Dr. Birnkrant
HFD-530/Dr. Jolson
HFD-530/Mr. Phi (via Teamlinks)
HFD-725/Dr. Elashoff
HFD-725/Dr. Flyer
HFD-725/Dr. Huque
HFD-725/Ms. Shores
This review contains 23 pages