

20977/S-002

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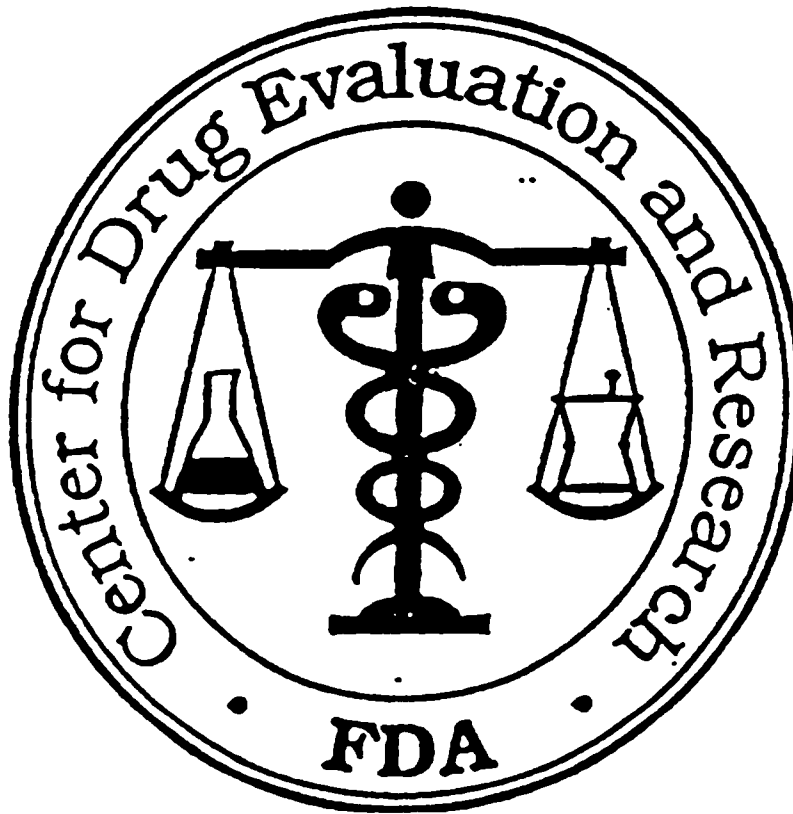
NDA 20-977 (S-002)
NDA 20-978 (S-002)

Ziagen®

(abacavir sulfate) Tablets and Oral Solution

These efficacy and labeling supplements include the addition of 48-week results from study CNAAB3005 and the results of the methadone/abacavir interaction study.

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**DIVISION OF ANTIVIRAL
DRUG PRODUCTS**

HFD-530

Imo Ibia, M.D.

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Medical Officers

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Regulatory Project Manager



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-977/S-002

NDA 20-978/S-002

Glaxo Wellcome Inc.
Attention: Martha Anne A. Moore, R.Ph.
Antiviral Group- Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

December 15, 2000

Dear Ms. Moore:

Please refer to your supplemental new drug applications, dated December 16, 1999, received December 17, 1999, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Ziagen® (abacavir sulfate) Tablets and Oral Solution.

We acknowledge receipt of your submissions dated: March 24, 2000; May 15, 2000; May 31, 2000; June 5, 2000; August 25, 2000; November 7, 2000; and December 5, 2000. The user fee goal date for these applications is December 17, 2000.

These supplemental new drug applications contain 48-week data from Study CAAB3005 comparing abacavir plus lamivudine plus zidovudine to indinavir plus lamivudine plus zidovudine and the results from the methadone/abacavir drug interaction study for inclusion in the abacavir label.

We have completed the review of these supplemental new drug applications, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to demonstrate that Ziagen® (abacavir sulfate) is safe and effective for use as recommended in the agreed upon draft labeling text dated December 5, 2000.

Accordingly, these applications are approved on the date of this letter. Marketing of these drug products and related activities continue to be in accordance with the accelerated approval regulations (21 CFR 314 Subpart H).

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert, text for the medication guide and text for the warning card dated December 5, 2000). Marketing the product with FPL that is not identical to the submitted labeling may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten copies on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format-NDAs* (January 1999). For administrative purposes these submissions should be designated "FINAL PRINTED LABELING" for approved supplement NDA 20-977 (S-002) and approved

supplement NDA 20-978 (S-002). Approval of these submissions by FDA is not required before the labeling is used.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that at this time you have fulfilled the pediatric study requirement for patients age 3 months to 16 years of age. In addition, we note that the requirement to study pediatric patients < 3 months of age has been waived.

We remind you that you must comply with the requirement for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have questions, please contact Ms. Melissa M. Truffa, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

Debra Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Debra Birnkrant

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NDA 20-977/S-002

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>20-977 / SE 8 - S-002</u>	
Drug <u>ZIGEN (abacavir) Tablets</u>	Applicant <u>Glaxo Wellcome</u>
<u>AND Oral Solution</u>	
RPM <u>MELISSA TRUFFA</u>	Phone <u>(301) 827-2335</u>
☒ 505(b)(1) ☐ 505(b)(2) Reference listed drug _____	
☐ Fast Track	☐ Rolling Review Review priority: ☒ S ☐ P
Pivotal IND(s) <u>45,331</u>	
Application classifications: Chem Class _____ Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>OCT 17, 2000</u> Secondary <u>DEC 17, 2000</u>

Arrange package in the following order:

Indicate N/A (not applicable),
X (completed), or add a
comment.

GENERAL INFORMATION:

- ◆ User Fee Information: ☒ User Fee Paid
☐ User Fee Waiver (attach waiver notification letter)
☐ User Fee Exemption

- ◆ Action Letter ☒ AP ☐ AE ☐ NA

- ◆ Labeling & Labels

FDA revised labeling and reviews.....	<u>X</u>
Original proposed labeling (package insert, patient package insert)	<u>X</u>
Other labeling in class (most recent 3) or class labeling.....	<u>NA</u>
Has DDMAC reviewed the labeling?	☐ Yes (include review) ☒ No
Immediate container and carton labels	<u>NA</u>
Nomenclature review	<u>NA</u>

- ◆ Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.

Exception for review (Center Director's memo).....	<u>NA</u>
OC Clearance for approval.....	<u>NA</u>

Continued ⇨

◆ Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review)	☐ Materials requested in AP letter
◆ Post-marketing Commitments	<u>NA</u>
Agency request for Phase 4 Commitments.....	<u>NA</u>
Copy of Applicant's commitments	<u>NA</u>
◆ Was Press Office notified of action (for approval action only)?.....	☐ Yes ☒ No
Copy of Press Release or Talk Paper.....	<u>NA</u>
◆ Patent	
Information [505(b)(1)]	<u>✓</u>
Patent Certification [505(b)(2)].....	<u>NA</u>
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	<u>NA</u>
◆ Exclusivity Summary	<u>✓</u>
◆ Debarment Statement	<u>✓</u>
◆ Financial Disclosure	
No disclosable information	<u> </u>
Disclosable information – indicate where review is located	<u> </u>
◆ Correspondence/Memoranda/Faxes	<u>✓</u>
◆ Minutes of Meetings	<u>NA</u>
Date of EOP2 Meeting <u>NA</u>	
Date of pre NDA Meeting <u>NA</u>	
Date of pre-AP Safety Conference <u>NA</u>	
◆ Advisory Committee Meeting	<u>NA</u>
Date of Meeting	<u>NA</u>
Questions considered by the committee	<u>NA</u>
Minutes or 48-hour alert or pertinent section of transcript	<u>NA</u>
◆ Federal Register Notices, DESI documents	<u>NA</u>

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	<u>X</u>
◆ Clinical review(s) and memoranda	<u>X</u>

Continued ⇨

- ◆ Safety Update review(s) NA
- ◆ Pediatric Information
 - ☒ Waiver/partial waiver (Indicate location of rationale for waiver) ☒ Deferred Pediatric Page..... X
 - ☐ Pediatric Exclusivity requested? ☐ Denied ☒ Granted ☐ Not Applicable
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) NA
 Recommendation for scheduling NA
- ◆ Microbiology (efficacy) review(s) and memoranda X
- ◆ DSI Audits NA
☐ Clinical studies ☐ bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ CMC review(s) and memoranda X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability NA
- ◆ DMF review(s) NA
- ◆ Environmental Assessment review/FONSI/Categorical exemption NA
- ◆ Micro (validation of sterilization) review(s) and memoranda NA
- ◆ Facilities Inspection (include EES report)
 Date completed NA ☐ Acceptable ☐ Not Acceptable
- ◆ Methods Validation NA ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ Pharm/Tox review(s) and memoranda X
- ◆ Memo from DSI regarding GLP inspection (if any) NA

- ◆ Statistical review(s) of carcinogenicity studies NA
- ◆ CAC/ECAC report NA

PRODUCT INFORMATION

ZIAGEN®

(abacavir sulfate)

Tablets

ZIAGEN®

(abacavir sulfate)

Oral Solution

WARNING: FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH THERAPY WITH ZIAGEN. PATIENTS DEVELOPING SIGNS OR SYMPTOMS OF HYPERSENSITIVITY (WHICH INCLUDE FEVER; SKIN RASH; FATIGUE; GASTROINTESTINAL SYMPTOMS SUCH AS NAUSEA, VOMITING, DIARRHEA, OR ABDOMINAL PAIN; AND RESPIRATORY SYMPTOMS SUCH AS PHARYNGITIS, DYSPNEA, OR COUGH) SHOULD DISCONTINUE ZIAGEN AS SOON AS A HYPERSENSITIVITY REACTION IS SUSPECTED. TO AVOID A DELAY IN DIAGNOSIS AND MINIMIZE THE RISK OF A LIFE-THREATENING HYPERSENSITIVITY REACTION, ZIAGEN SHOULD BE PERMANENTLY DISCONTINUED IF HYPERSENSITIVITY CAN NOT BE RULED OUT, EVEN WHEN OTHER DIAGNOSES ARE POSSIBLE (E.G., ACUTE ONSET RESPIRATORY DISEASES, GASTROENTERITIS, OR REACTIONS TO OTHER MEDICATIONS).

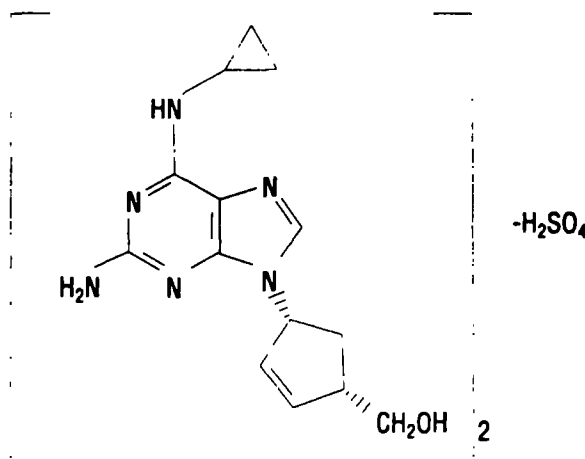
ZIAGEN SHOULD NOT BE RESTARTED FOLLOWING A HYPERSENSITIVITY REACTION BECAUSE MORE SEVERE SYMPTOMS WILL RECUR WITHIN HOURS AND MAY INCLUDE LIFE-THREATENING HYPOTENSION AND DEATH.

SEVERE OR FATAL HYPERSENSITIVITY REACTIONS CAN OCCUR WITHIN HOURS AFTER REINTRODUCTION OF ZIAGEN IN PATIENTS WHO HAVE NO IDENTIFIED HISTORY OR UNRECOGNIZED SYMPTOMS OF HYPERSENSITIVITY TO ABACAVIR THERAPY (see WARNINGS, PRECAUTIONS: Information for Patients, and ADVERSE REACTIONS).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIAGEN AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

DESCRIPTION: ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV. The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with 1*S*, 4*R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient ($\log P$) of approximately 1.20 at 25°C.

ZIAGEN Tablets are for oral administration. Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir and the inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hydroxypropyl methylcellulose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

ZIAGEN Oral Solution is for oral administration. One milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (20 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), and sorbitol solution.

In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages for ZIAGEN are expressed in terms of abacavir.

MICROBIOLOGY:

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate. Carbovir

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

64 triphosphate is an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate
65 inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural
66 substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the
67 incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage
68 essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

69 **Antiviral Activity *In Vitro*:** The *in vitro* anti-HIV-1 activity of abacavir was evaluated against a
70 T-cell tropic laboratory strain HIV-1 IIIB in lymphoblastic cell lines, a monocyte/macrophage tropic
71 laboratory strain HIV-1 BaL in primary monocytes/macrophages, and clinical isolates in peripheral
72 blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50
73 percent (IC₅₀) ranged from 3.7 to 5.8 µM against HIV-1 IIIB, and was 0.26 ± 0.18 µM
74 (1 µM = 0.28 mcg/mL) against 8 clinical isolates. The IC₅₀ of abacavir against HIV-1 BaL varied
75 from 0.07 to 1.0 µM. Abacavir had synergistic activity in combination with amprenavir, nevirapine,
76 and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and
77 zalcitabine *in vitro*. These drug combinations have not been adequately studied in humans. The
78 relationship between *in vitro* susceptibility of HIV to abacavir and the inhibition of HIV replication in
79 humans has not been established.

80 **Drug Resistance:** HIV-1 isolates with reduced sensitivity to abacavir have been selected *in vitro*
81 and were also obtained from patients treated with abacavir. Genetic analysis of isolates from
82 abacavir-treated patients showed point mutations in the reverse transcriptase gene that resulted
83 in amino acid substitutions at positions K65R, L74V, Y115F, and M184V. Phenotypic analysis of
84 HIV-1 isolates that harbored abacavir-associated mutations from 17 patients after 12 weeks of
85 abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir *in vitro*.

86 Genetic analysis of HIV-1 isolates from 21 previously antiretroviral therapy-naïve patients with
87 confirmed virologic failure (plasma HIV-1 RNA ≥400 copies/mL) after 16 to 48 weeks of
88 abacavir/lamivudine/zidovudine therapy showed that 16/21 isolates had
89 abacavir/lamivudine-associated mutation M184V, either alone (11/21), or in combination with
90 Y115F (1/21) or zidovudine-associated (4/21) mutations at the last time point. Phenotypic data
91 available on isolates from 10 patients showed that 7 of the 10 isolates had 25- to 86-fold
92 decreases in susceptibility to lamivudine *in vitro*. Likewise, isolates from 2 of these 7 patients had
93 7- to 10-fold decreases in susceptibility to abacavir *in vitro*. The clinical relevance of genotypic and
94 phenotypic changes associated with abacavir therapy has not been established, but is currently
95 under evaluation.

96 **Cross-Resistance:** Recombinant laboratory strains of HIV-1 (HXB2) containing multiple reverse
97 transcriptase mutations conferring abacavir resistance exhibited cross-resistance to lamivudine,
98 didanosine, and zalcitabine *in vitro*. For clinical information in treatment-experienced patients, see
99 INDICATIONS AND USAGE: Description of Clinical Studies and PRECAUTIONS.

100

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

CLINICAL PHARMACOLOGY:

Pharmacokinetics in Adults: The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-infected adult patients after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1200 mg/day.

Absorption and Bioavailability: Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 mcg/mL (mean $\pm$ SD) and $AUC_{(0-12\ h)}$ was 6.02 ± 1.73 mcg·h/mL. Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC_{∞}) in the fed and fasting states; therefore, ZIAGEN Tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of ZIAGEN Oral Solution and ZIAGEN Tablets. Therefore, these products may be used interchangeably.

Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF $AUC_{(0-6\ h)}$ to plasma abacavir $AUC_{(0-6\ h)}$ ratio ranged from 27% to 33%.

Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

Metabolism: In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the 5'-glucuronide). The metabolites do not have antiviral activity. *In vitro* experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

Elimination: Elimination of abacavir was quantified in a mass balance study following administration of a 600-mg dose of ^{14}C -abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5'-carboxylic acid metabolite, 36% as the 5'-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose studies, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L/hr per kg (mean $\pm$ SD).

Special Populations: Adults With Impaired Renal Function: The pharmacokinetic properties of ZIAGEN have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

137 **Pediatric Patients:** The pharmacokinetics of abacavir have been studied after either single or
138 repeat doses of ZIAGEN in 68 pediatric patients. Following multiple-dose administration of
139 ZIAGEN 8 mg/kg twice daily, steady-state $AUC_{(0-12\text{ h})}$ and $C_{\max}$ were 9.8 ± 4.56 mcg•h/mL and
140 3.71 ± 1.36 mcg/mL (mean $\pm$ SD), respectively (see PRECAUTIONS: Pediatric Use).

141 **Geriatric Patients:** The pharmacokinetics of ZIAGEN have not been studied in patients over
142 65 years of age.

143 **Gender:** The pharmacokinetics of ZIAGEN with respect to gender have not been determined.

144 **Race:** The pharmacokinetics of ZIAGEN with respect to race have not been determined.

145 **Drug Interactions:** In human liver microsomes, abacavir did not inhibit cytochrome P450
146 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug
147 interactions will occur between abacavir and drugs metabolized through these pathways.

148 Due to their common metabolic pathways via glucuronyl transferase with zidovudine,
149 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir
150 (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis
151 showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of
152 lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure
153 (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically
154 relevant changes with concurrent abacavir.

155 Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic
156 interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each
157 patient received the following treatments on separate occasions: a single 600-mg dose of
158 abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg
159 ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC_{∞}
160 and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no effect on the pharmacokinetic
161 properties of ethanol, so no clinically significant interaction is expected in men. This interaction
162 has not been studied in females.

163 **Methadone:** In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy
164 (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the current recommended
165 dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not
166 result in a methadone dose modification in the majority of patients; however, an increased
167 methadone dose may be required in a small number of patients.

168

169 **INDICATIONS AND USAGE:** ZIAGEN Tablets and Oral Solution, in combination with other
170 antiretroviral agents, are indicated for the treatment of HIV-1 infection. This indication is
171 based on 2 controlled trials of 16 and 48 weeks' duration that evaluated suppression of HIV
172 RNA and changes in CD4 cell count. At present, there are no results from controlled trials

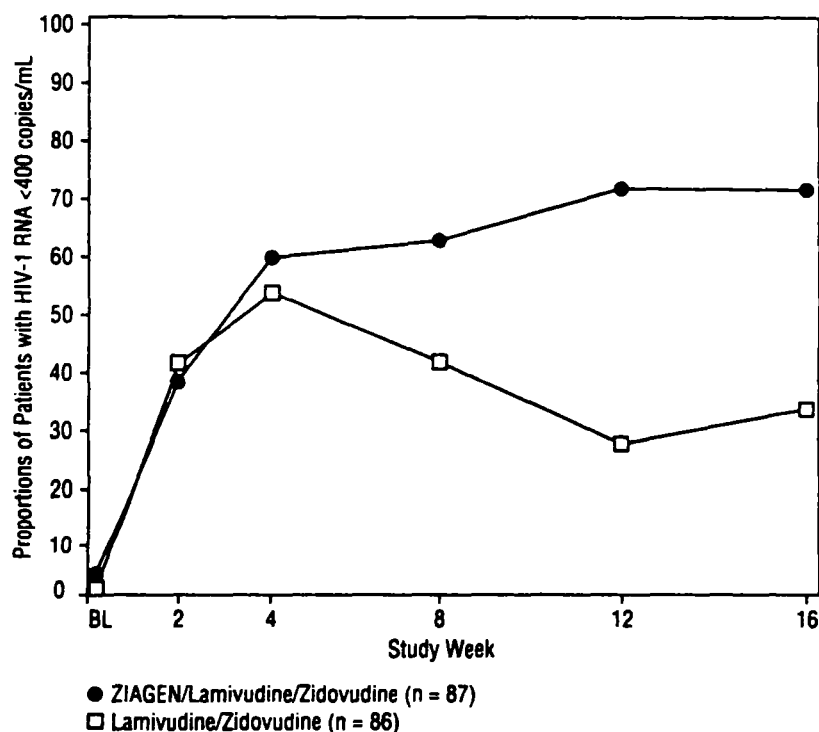
ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

173 evaluating the effect of ZIAGEN on clinical progression of HIV (see Description of Clinical
 174 Studies).

175 **Description of Clinical Studies: Therapy-Naive Adults:** CNAAB3003 is a multicenter,
 176 double-blind, placebo-controlled study in which 173 HIV-infected, therapy-naive adults were
 177 randomized to receive either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and
 178 zidovudine (300 mg twice daily) or lamivudine (150 mg twice daily) and zidovudine (300 mg twice
 179 daily). The duration of double-blind treatment was 16 weeks. Study participants were: male (76%),
 180 Caucasian (54%), African-American (28%), and Hispanic (16%). The median age was 34 years,
 181 the median pretreatment CD4 cell count was 450 cells/mm³, and median plasma HIV-1 RNA was
 182 4.5 log₁₀ copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using
 183 Roche Amplicor HIV-1 MONITOR® Test) through 16 weeks of treatment are summarized in
 184 Figure 1.

185

186 **Figure 1: Proportions of Patients with HIV-1 RNA <400 copies/mL in Study CNAAB3003¹**



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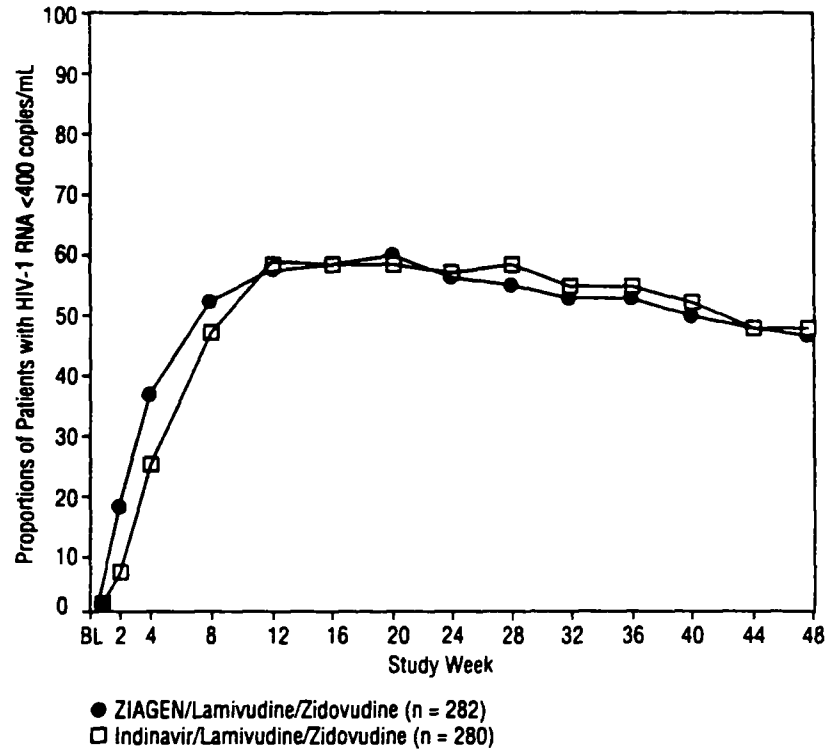
189 After 16 weeks of therapy, the median CD4 increases from baseline were 47 cells/mm³ in the
 190 group receiving ZIAGEN and 112 cells/mm³ in the placebo group.

191 CNAAB3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected,
 192 therapy-naive adults with a pre-entry plasma HIV-1 RNA >10,000 copies/mL were randomized to
 193 receive either ZIAGEN (300 mg twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine
 194 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. Study

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

participants were male (87%), Caucasian (73%), African-American (15%), and Hispanic (9%). At baseline the median age was 36 years, the median pretreatment CD4 cell count was 360 cells/mm³, and median plasma HIV-1 RNA was 4.8 log₁₀ copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using Roche Amplicor HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Figure 2.

Figure 2: Proportions of Patients with HIV-1 RNA <400 copies/mL in Study CNAAB3005¹



¹Discontinuations of randomized therapy or missing data were considered as HIV-1 RNA ≥400 copies/mL.

Through week 48, an overall mean increase in CD4 cells of about 150 cells/mm³ was observed in both treatment arms.

Table 1: Outcomes of Randomized Treatment Through Week 48 (CNAAB3005)

Outcome	ZIAGEN/Lamivudine/ Zidovudine (n = 282)	Indinavir/ Lamivudine/Zidovudine (n = 280)
HIV RNA <400 copies/mL	46%	47%
HIV RNA ≥400 copies/mL	29%	28%
CDC Class C event	2%	<1%
Discontinued due to adverse reactions	9%	11%
Discontinued due to other reasons [†]	6%	6%
Randomized but never initiated treatment	7%	5%

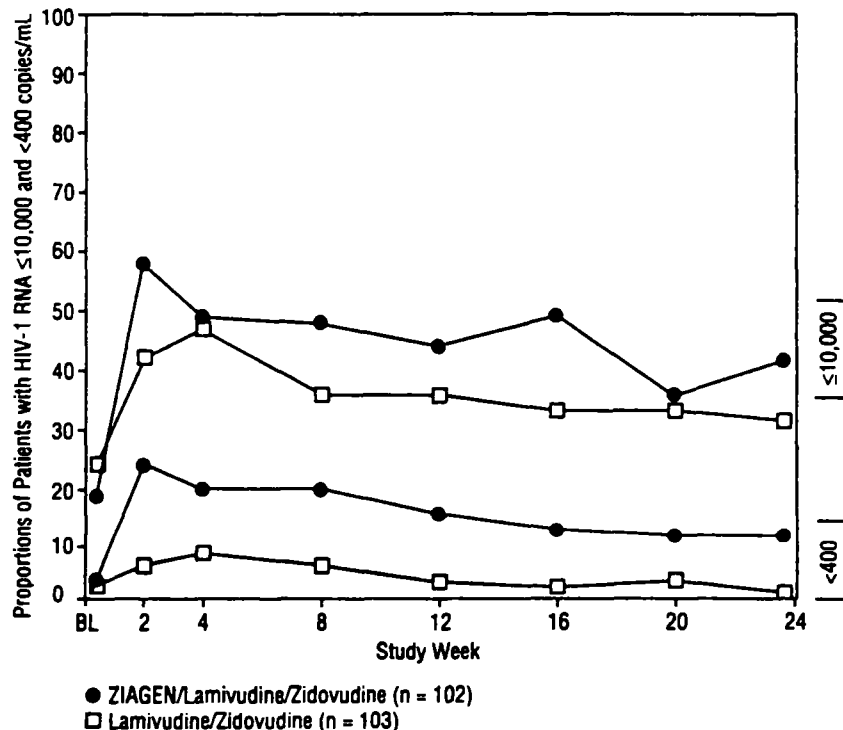
[†]Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.

[†]Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other.

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

Therapy-Experienced Pediatric Patients: CNA3006 is a randomized, double-blind study comparing ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m² twice daily versus lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily. Two hundred and five pediatric patients were enrolled: female (56%), Caucasian (17%), African-American (50%), Hispanic (30%), median age of 5.4 years, baseline CD4 cell percent >15% (median = 27%), and median baseline plasma HIV-1 RNA of 4.6 log₁₀ copies/mL. Eighty percent and 55% of patients had prior therapy with zidovudine and lamivudine, respectively, most often in combination. The median duration of prior nucleoside analogue therapy was 2 years. Proportions of patients with plasma HIV-1 RNA levels ≤10,000 and <400 copies/mL, respectively, through 24 weeks of treatment are summarized in Figure 3.

Figure 3: Proportions of Patients with Plasma HIV-1 RNA ≤10,000 copies/mL or <400 copies/mL Through Week 24 in Study CNA3006^{1,2}



¹Missing data were considered as above the HIV-1 RNA threshold.

²No significant difference was observed at 24 weeks for the ≤10,000 copies/mL threshold.

After 16 weeks of therapy, the median CD4 increases from baseline were 69 cells/mm³ in the group receiving ZIAGEN and 9 cells/mm³ in the control group.

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

230 **CONTRAINDICATIONS: Abacavir sulfate has been associated with fatal hypersensitivity**
231 **reactions. ZIAGEN SHOULD NOT BE RESTARTED FOLLOWING A HYPERSENSITIVITY**
232 **REACTION TO ABACAVIR (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS).**

233 ZIAGEN Tablets and Oral Solution are contraindicated in patients with previously
234 demonstrated hypersensitivity to any of the components of the products (see WARNINGS).

235
236 **WARNINGS:**

237 **Hypersensitivity Reaction: Fatal hypersensitivity reactions have been associated with**
238 **therapy with ZIAGEN. Patients developing signs or symptoms of hypersensitivity (which**
239 **include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting,**
240 **diarrhea, or abdominal pain; and respiratory symptoms such as pharyngitis, dyspnea, or**
241 **cough) should discontinue ZIAGEN as soon as a hypersensitivity reaction is first**
242 **suspected, and should seek medical evaluation immediately. To avoid a delay in diagnosis**
243 **and minimize the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be**
244 **permanently discontinued if hypersensitivity can not be ruled out, even when other**
245 **diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions**
246 **to other medications).**

247 **ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more**
248 **severe symptoms will recur within hours and may include life-threatening hypotension and**
249 **death.**

250 **Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of**
251 **ZIAGEN in patients who have no identified history or unrecognized symptoms of**
252 **hypersensitivity to abacavir therapy.**

253 When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a
254 hypersensitivity reaction, and if reinitiation of therapy is under consideration, the reason for
255 discontinuation should be evaluated to ensure that the patient did not have symptoms of a
256 hypersensitivity reaction. If hypersensitivity can not be ruled out, abacavir should **NOT** be
257 reintroduced. If symptoms consistent with hypersensitivity are not identified, reintroduction can be
258 undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Patients should
259 be made aware that a hypersensitivity reaction can occur with reintroduction of abacavir, and that
260 abacavir reintroduction should be undertaken only if medical care can be readily accessed by the
261 patient or others (see ADVERSE REACTIONS).

262 In clinical trials, hypersensitivity reactions have been reported in approximately 5% of adult and
263 pediatric patients receiving abacavir. Symptoms usually appear within the first 6 weeks of
264 treatment with ZIAGEN although these reactions may occur at any time during therapy (see
265 **PRECAUTIONS: Information for Patients and ADVERSE REACTIONS).**

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Abacavir Hypersensitivity Reaction Registry: To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering ZIAGEN to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with ZIAGEN should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

PRECAUTIONS:

General: Abacavir should always be used in combination with other antiretroviral agents. Abacavir should not be added as a single agent when antiretroviral regimens are changed due to loss of virologic response.

Therapy-Experienced Patients: In clinical trials, patients with prolonged prior nucleoside reverse transcriptase inhibitor (NRTI) exposure or who had HIV-1 isolates that contained multiple mutations conferring resistance to NRTIs had limited response to abacavir. The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients (see MICROBIOLOGY: Cross-Resistance).

Information for Patients: Patients should be advised that a Medication Guide and Warning Card summarizing the symptoms of abacavir hypersensitivity reactions should be dispensed by the pharmacist with each new prescription and refill of ZIAGEN. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be instructed to carry the Warning Card with them.

Patients should be advised of the possibility of a hypersensitivity reaction to ZIAGEN that may result in death. Patients developing signs or symptoms of hypersensitivity (which include fever; skin rash; fatigue; gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain; and respiratory symptoms such as sore throat, shortness of breath, or cough) should discontinue treatment with ZIAGEN and seek medical evaluation immediately. **ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.** Patients who have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply) should be made aware that a severe or fatal hypersensitivity reaction can occur with reintroduction of abacavir. Patients should be instructed not to reintroduce abacavir without medical consultation and that reintroduction of abacavir should

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be undertaken only if medical care can be readily accessed by the patient or others (see ADVERSE REACTIONS and WARNINGS).

ZIAGEN is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using ZIAGEN. Patients should be advised that the use of ZIAGEN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised that the long-term effects of ZIAGEN are unknown at this time.

ZIAGEN Tablets and Oral Solution are for oral ingestion only.

Patients should be advised of the importance of taking ZIAGEN exactly as it is prescribed.

Drug Interactions: Pharmacokinetic properties of abacavir were not altered by the addition of either lamivudine or zidovudine or the combination of lamivudine and zidovudine. No clinically significant changes to lamivudine or zidovudine pharmacokinetics were observed following concomitant administration of abacavir.

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure (see CLINICAL PHARMACOLOGY: Drug Interactions).

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the current recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%) This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. At systemic exposures approximately 9 times higher than that in humans at the therapeutic dose, abacavir was clastogenic in males and not clastogenic in females in an *in vivo* mouse bone marrow micronucleus assay.

Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Abacavir had no adverse effects on the mating performance or fertility of male and female rats at doses of up to 500 mg/kg per day, a dose expected to produce exposures approximately 8-fold higher than that in humans at the therapeutic dose based on body surface area comparisons.

Pregnancy: Pregnancy Category C. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal

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malformations were observed when rats were treated with abacavir at doses of 1000 mg/kg during organogenesis. This dose produced 35 times the human exposure, based on AUC. In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg per day. The offspring of female rats treated with abacavir at 500 mg/kg per day (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 700 mg/kg (8.5 times the human exposure at the recommended dose, based on AUC).

There are no adequate and well-controlled studies in pregnant women. ZIAGEN should be used during pregnancy only if the potential benefits outweigh the risk.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to ZIAGEN, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

Although it is not known if abacavir is excreted in human milk, abacavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving ZIAGEN.**

Pediatric Use: The safety and effectiveness of ZIAGEN have been established in pediatric patients aged 3 months to 13 years. Use of ZIAGEN in these age groups is supported by pharmacokinetic studies and evidence from adequate and well-controlled studies of ZIAGEN in adults and pediatric patients (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Pediatric Patients; INDICATIONS AND USAGE: Description of Clinical Studies; WARNINGS; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION).

Geriatric Use: Clinical studies of ZIAGEN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:

Hypersensitivity Reaction: Fatal hypersensitivity reactions have been associated with therapy with ZIAGEN. Therapy with ZIAGEN SHOULD NOT be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Patients developing signs or symptoms of hypersensitivity should discontinue treatment as soon as a hypersensitivity reaction is

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first suspected, and should seek medical evaluation immediately. To avoid a delay in diagnosis and minimize the risk of a life-threatening hypersensitivity reaction, ZIAGEN should be permanently discontinued if hypersensitivity can not be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases, gastroenteritis, or reactions to other medications).

Severe or fatal hypersensitivity reactions can occur within hours after reintroduction of ZIAGEN in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy (see WARNINGS and PRECAUTIONS: Information for Patients).

When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity can not be ruled out, abacavir should **NOT** be reintroduced. If symptoms consistent with hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of hypersensitivity reaction. Patients should be made aware that a hypersensitivity reaction can occur with reintroduction of abacavir, and that abacavir reintroduction should be undertaken only if medical care can be readily accessed by the patient or others (see WARNINGS).

In clinical studies, approximately 5% of adult and pediatric patients receiving ZIAGEN developed a hypersensitivity reaction. This reaction is characterized by the appearance of symptoms indicating multi-organ/body system involvement. Symptoms usually appear within the first 6 weeks of treatment with ZIAGEN, although these reactions may occur at any time during therapy. Frequently observed signs and symptoms include fever; skin rash; fatigue; and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Other signs and symptoms include malaise, lethargy, myalgia, myolysis, arthralgia, edema, pharyngitis, cough, dyspnea, headache, and paresthesia. Some patients who experienced a hypersensitivity reaction were initially thought to have acute onset or worsening respiratory disease. The diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of acute onset respiratory diseases, even if alternative respiratory diagnoses (pneumonia, bronchitis, pharyngitis, or flu-like illness) are possible.

Physical findings include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial but may be variable in appearance. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities include elevated liver function tests, increased creatine phosphokinase or creatinine, and lymphopenia. Anaphylaxis, liver failure, renal failure, hypotension, and death have occurred in association with hypersensitivity reactions. Symptoms worsen with continued therapy but often resolve upon discontinuation of ZIAGEN.

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Risk factors that may predict the occurrence or severity of hypersensitivity to abacavir have not been identified.

Therapy-Naive Adults: Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with lamivudine 150 mg twice daily and zidovudine 300 mg twice daily from CNAAB3003 are listed in Table 2.

**Table 2: Selected Clinical Adverse Events Grades 1-4 ($\geq 5\%$ Frequency)
in Therapy-Naive Adults (CNAAB3003) Through 16 Weeks of Treatment**

Adverse Event	ZIAGEN/Lamivudine/Zidovudine (n = 83)	Lamivudine/Zidovudine (n = 81)
Nausea	47%	41%
Nausea and vomiting	16%	11%
Diarrhea	12%	11%
Loss of appetite/anorexia	11%	10%
Insomnia and other sleep disorders	7%	5%

Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily compared with indinavir 800 mg 3 times daily, lamivudine 150 mg twice daily, and zidovudine 300 mg twice daily from CNAAB3005 are listed in Table 3.

**Table 3: Selected Clinical Adverse Events Grades 1-4 ($\geq 5\%$ Frequency)
in Therapy-Naive Adults (CNAAB3005) Through 48 Weeks of Treatment**

Adverse Event	ZIAGEN/Lamivudine/Zidovudine (n = 262)	Indinavir/Lamivudine/Zidovudine (n = 264)
Nausea	60%	61%
Nausea and vomiting	30%	27%
Diarrhea	26%	27%
Loss of appetite/anorexia	15%	11%
Insomnia and other sleep disorders	13%	12%
Fever and/or chills	20%	13%
Headache	28%	25%
Malaise and/or fatigue	44%	41%

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Five subjects in the abacavir arm of study CNAAB3005 experienced worsening of pre-existing depression compared to none in the indinavir arm. The background rates of pre-existing depression were similar in the 2 treatment arms.

Pediatric Patients: Selected clinical adverse events with a $\geq 5\%$ frequency during therapy with ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m² twice daily compared with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m² twice daily from CNAAB3006 are listed in Table 4.

**Table 4: Selected Clinical Adverse Events Grades 1-4 ($\geq 5\%$ Frequency)
in Therapy-Experienced Pediatric Patients (CNAAB3006) Through 16 Weeks of Treatment**

Adverse Event	ZIAGEN/Lamivudine/Zidovudine (n = 102)	Lamivudine/Zidovudine (n = 103)
Nausea and vomiting	38%	18%
Fever	19%	12%
Headache	16%	12%
Diarrhea	16%	15%
Skin rashes	11%	8%
Loss of appetite/anorexia	9%	2%

Laboratory Abnormalities: Laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies in the 2 treatment groups in studies CNAAB3003 and CNAAB3006. Mild elevations of blood glucose were more frequent in subjects receiving abacavir. In study CNAAB3003, triglyceride elevations (all grades) were more common on the abacavir arm (25%) than on the placebo arm (11%). In study CNAAB3005, hyperglycemia and disorders of lipid metabolism occurred with similar frequency in the abacavir and indinavir treatment arms.

Other Adverse Events: In addition to adverse events in Tables 2, 3, and 4, other adverse events observed in the expanded access program were pancreatitis and increased GGT.

OVERDOSAGE: There is no known antidote for ZIAGEN. It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION: A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill. To facilitate reporting of hypersensitivity reactions and collection of information on each case, an Abacavir Hypersensitivity Registry has been established. Physicians should register patients by calling 1-800-270-0425.

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464 ZIAGEN may be taken with or without food.

465 **Adults:** The recommended oral dose of ZIAGEN for adults is 300 mg twice daily in combination
466 with other antiretroviral agents.

467 **Adolescents and Pediatric Patients:** The recommended oral dose of ZIAGEN for adolescents
468 and pediatric patients 3 months to up to 16 years of age is 8 mg/kg twice daily (up to a maximum
469 of 300 mg twice daily) in combination with other antiretroviral agents.

470 **Dose Adjustment in Hepatic Impairment:** Insufficient data are available to recommend a
471 dosage of ZIAGEN in patients with hepatic impairment.

472

473 **HOW SUPPLIED:** ZIAGEN is available as tablets and oral solution.

474 **ZIAGEN Tablets:** Each tablet contains abacavir sulfate equivalent to 300 mg abacavir. The
475 tablets are yellow, biconvex, capsule-shaped, film-coated, and imprinted with "GX 623" on one
476 side with no marking on the reverse side. They are packaged as follows:

477 Bottles of 60 tablets (NDC 0173-0661-01).

478 Unit dose blister packs of 60 tablets (NDC 0173-0661-00). Each pack contains 6 blister cards of
479 10 tablets each.

480 **Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP).**

481 **ZIAGEN Oral Solution:** It is a clear to opalescent, yellowish, strawberry-banana-flavored liquid.
482 Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged
483 in plastic bottles as follows:

484 Bottles of 240 mL (NDC 0173-0664-00) with child-resistant closure. This product does not require
485 reconstitution.

486 **Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP). DO NOT**
487 **FREEZE. May be refrigerated.**

488

489

490 **GlaxoWellcome**

491 Glaxo Wellcome Inc.

492 Research Triangle Park, NC 27709

493

494 US Patent Nos. 5,034,394 and 5,089,500

495

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497

498 Date of Issue

RL-no.

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

MEDICATION GUIDE

ZIAGEN® (z-EYE-uh-jen) (abacavir sulfate) Tablets and Oral Solution

Generic name: abacavir (uh-BACK-ah-veer) sulfate tablets and oral solution

Read the Medication Guide you get each time you fill your prescription for Ziagen. There may be new information since you filled your last prescription.

What is the most important information I should know about Ziagen?

About 1 in 20 patients (5%) who take Ziagen will have a **serious allergic reaction** (hypersensitivity reaction) **that may cause death if the drug is not stopped right away.**

You may be having this reaction if:

- (1) you get a skin rash, or**
- (2) you get 1 or more symptoms from at least 2 of the following groups:**
 - **Fever**
 - **Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
 - **Extreme tiredness, achiness, generally ill feeling**
 - **Sore throat, shortness of breath, cough**

If you think you may be having a reaction, **STOP taking Ziagen and call your doctor right away.**

If you stop treatment with Ziagen because of this serious reaction, **NEVER take Ziagen (abacavir) again.** If you take Ziagen again after you have had this serious reaction, **you could die within hours.**

Some patients who have stopped taking Ziagen (abacavir) and who have then started taking Ziagen (abacavir) again have had serious or life-threatening allergic (hypersensitivity) reactions. If you must stop treatment with Ziagen for reasons other than symptoms of hypersensitivity, do not begin taking it again without talking to your health care provider. If your health care provider decides that you may begin taking Ziagen again, you should do so only in a setting with other people to get access to a doctor if needed.

A written list of these symptoms is on the Warning Card your pharmacist gives you. Carry this Warning Card with you.

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Ziagen can have other serious side effects. Be sure to read the section below titled "What are the possible side effects of Ziagen?"

508

509 **What is Ziagen?**

510 Ziagen is a medication used to treat HIV infection. Ziagen is taken by mouth as a tablet or a
511 strawberry-banana-flavored liquid. Ziagen is a medicine called a nucleoside analogue reverse
512 transcriptase inhibitor (NRTI). Ziagen is only proven to work when taken in combination with other
513 anti-HIV medications. When used in combination with these other medications, Ziagen helps
514 lower the amount of HIV found in your blood. This helps to keep your immune system as healthy
515 as possible so that it can help fight infection.

516

517 Ziagen does not cure HIV infection or AIDS. Ziagen has not been studied long enough to know if it
518 will help you live longer or have fewer of the medical problems that are associated with HIV
519 infection or AIDS. Therefore, you must see your health care provider regularly.

520

521 **Who should not take Ziagen?**

522 Do not take Ziagen if you have ever had a serious allergic reaction (a hypersensitivity reaction) to
523 abacavir (as Ziagen or Trizivir™ [abacavir, lamivudine, and zidovudine] Tablets). If you have had
524 such a reaction, return all of your unused Ziagen to your doctor or pharmacist.

525

526 **How should I take Ziagen?**

527 To help make sure that your anti-HIV therapy is as effective as possible, take your Ziagen exactly
528 as your doctor prescribes it. Do not skip any doses.

529

530 The usual dosage for adults (at least 16 years of age) is one 300-mg tablet twice a day. You can
531 take Ziagen with food or on an empty stomach.

532

533 Adolescents and children 3 months and older can also take Ziagen. Your doctor will tell you if the
534 oral solution or tablet is best for your child. Also, your child's doctor will decide the right dose
535 based on your child's weight and age. Ziagen has not been studied in children under 3 months of
536 age.

537

538 If you miss a dose of Ziagen, take the missed dose right away. Then, take the next dose at the
539 usual scheduled time. Do not let your Ziagen run out. The amount of virus in your blood may
540 increase if your anti-HIV drugs are stopped, even for a short time. Also, the virus in your body may
541 become harder to treat.

542

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543 What should I avoid while taking Ziagen?

544 Practice safe sex while using Ziagen. Do not use or share dirty needles. Ziagen does not reduce
545 the risk of passing HIV to others through sexual contact or blood contamination.

546

547 Talk to your doctor if you are pregnant or if you become pregnant while taking Ziagen. Ziagen has
548 not been studied in pregnant women. It is not known whether Ziagen will harm the unborn child.

549

550 Mothers with HIV should not breastfeed their babies because HIV is passed to the baby in breast
551 milk. Also Ziagen can be passed to babies in breast milk and could cause the child to have side
552 effects.

553

554 What are the possible side effects of Ziagen?

555 **Life-threatening allergic reaction.** Ziagen has caused some people to have a life-threatening
556 reaction (hypersensitivity reaction) that can cause death. How to recognize a possible reaction,
557 and what to do are discussed in "What is the most important information I should know about
558 Ziagen?" at the beginning of this Medication Guide.

559

560 **Lactic Acidosis and severe liver problems.** Ziagen can cause a serious condition called lactic
561 acidosis and, in some cases, this condition can cause death. Nausea and tiredness that don't get
562 better may be symptoms of lactic acidosis. Women are more likely than men to get this rare but
563 serious side effect.

564

565 Ziagen can cause other side effects. In studies, the most common side effects with Ziagen were
566 nausea, vomiting, malaise or fatigue, headache, diarrhea, and loss of appetite. Most of these side
567 effects did not cause people to stop taking Ziagen.

568

569 This listing of side effects is not complete. Your doctor or pharmacist can discuss with you a more
570 complete list of side effects with Ziagen.

571

572 Ask a health care professional about any concerns about Ziagen. If you want more information,
573 ask your doctor or pharmacist for the labeling for Ziagen that was written for health care
574 professionals.

575

576 Do not use Ziagen for a condition for which it was not prescribed. Do not give Ziagen to other
577 persons.

578

579

580 **GlaxoWellcome**

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ZIAGEN® (abacavir sulfate) Oral Solution

581 Glaxo Wellcome Inc.

582 Research Triangle Park, NC 27709

583

584 Date of Issue

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586 *This Medication Guide has been approved by the US Food and Drug Administration.*

587

ZIAGEN® (abacavir sulfate) Tablets
ZIAGEN® (abacavir sulfate) Oral Solution

(Front of card)

WARNING CARD

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

Patients taking Ziagen may have a hypersensitivity reaction (a serious allergic reaction) **that can be life-threatening. IF YOU NOTICE A SKIN RASH OR TWO OR MORE OF THE FOLLOWING SETS OF SYMPTOMS WHILE TAKING ZIAGEN, STOP TAKING IT AND CALL YOUR DOCTOR IMMEDIATELY.**

- fever
- nausea, vomiting, diarrhea, or abdominal pain
- severe tiredness, achiness, or generally ill feeling
- sore throat, shortness of breath, or cough

You should carry this Warning Card with you.

(Back of Card)

WARNING CARD

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

If you must stop treatment with Ziagen because you have had this serious reaction, **NEVER** take Ziagen again. If you take Ziagen again after you have had this serious reaction, **WITHIN HOURS** you may experience life-threatening symptoms that may include lowering of your blood pressure or death.

You should return all of your unused Ziagen to your doctor or pharmacist for proper disposal.

Please read the Medication Guide for additional information on Ziagen.

month, 2000	item #	barcode
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42 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

GlaxoWellcome

December 10, 1999

Bank Mellon, N/A
Bank @ FDA
Food and Drug Administration
27th Floor (FDA 360909)
Three Mellon Bank Center
Pittsburgh, PA 15259-0001

Re: NDA 20-977; ZIAGEN® (abacavir sulfate) Tablets
NDA 20-978; ZIAGEN® (abacavir sulfate) Oral Solution
User Fee: With Clinical Data

Please find enclosed Glaxo Wellcome check number 1619409 in the amount of \$136,141.00. This initial payment is 100% of the application fee for the Supplemental New Drug Application that is being filed with the Center for Drug Evaluation and Research, FDA, Division of Antiviral Drug Products. Please note the User Fee ID Number for this submission is 3867.

Please find below requested information regarding this application.

Type of Application:	New Drug Application with Clinical Data	
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	X

Should you have any questions, please contact me at (919) 483-9347. Thank you.

Sincerely,



Martha Anne A. Moore, R.Ph.
Antiviral Group – Regulatory Affairs

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709		3. PRODUCT NAME Ziagen® (abacavir sulfate) Tablets	
2. TELEPHONE NUMBER (Include Area Code) (919) 483-2100		4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? yes IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: ☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. ☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).	
5. USER FEE I.D. NUMBER 3867		6. LICENSE NUMBER / NDA NUMBER NDA 20-977	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.			
☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) ☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.) ☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) ☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act (See item 7, reverse side before checking box.) ☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) FOR BIOLOGICAL PRODUCTS ONLY ☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION ☐ A CRUDE ALLERGENIC EXTRACT PRODUCT ☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY ☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT ☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO (See reverse side if answered YES)			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.			
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:			
DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0297) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.	
Please DO NOT RETURN this form to this address.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Martha Anne A. Moore</i> Martha Anne A. Moore		TITLE Antiviral Group, Regulatory Affairs	DATE December 10, 1999

Supplemental New Drug Application

NDA 20-977 ZIAGEN® (abacavir sulfate) Tablets
NDA 20-978 ZIAGEN® (abacavir sulfate) Oral Solution

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller
Head, Clinical Compliance
World Wide Compliance

13 DEC 1999

Date

ITEM 13

PATENT INFORMATION

for

**sNDA 20-977
ZIAGEN™ (abacavir sulfate) Tablets**

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Ziagen™ Tablets
Active Ingredient:	abacavir sulfate
Strength(s):	300 mg
Dosage Form:	Tablet
sNDA Number:	20-977

Applicable Patent Numbers and Expiration Dates:

Patent No.	5,034,394
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Composition Formulation
Patent No.	5,089,500
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Method of Use (treatment of viral infections, HIV, HBV)

The undersigned declares that U.S. Patent Nos. 5,034,394 and 5,089,500

cover the composition, formulation, and methods of use of ZIAGEN™ (abacavir sulfate) Tablets. These U.S. patents should be included in Item 13 of sNDA 20-977.

August 3, 1999
Date

Karen L. Prus
Karen L. Prus, Ph.D.
Registered Patent Attorney
Registration No. 39,337

ITEM 13

PATENT INFORMATION

for

**sNDA 20-978
ZIAGEN™ (abacavir sulfate) Oral Solution**

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Ziagen™ Oral Solution
Active Ingredient:	abacavir sulfate
Strength(s):	20 mg/mL
Dosage Form:	Oral Solution
sNDA Number:	20-978

Applicable Patent Numbers and Expiration Dates:

Patent No.	5,034,394
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Composition Formulation
Patent No.	5,089,500
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Methods of Use (treatment of viral infections, HIV, HBV)

The undersigned declares that U.S. Patent Nos. 5,034,394 and 5,089,500

cover the composition, formulation, and methods of use of ZIAGEN™ (abacavir sulfate) Oral Solution. These U.S. patents should be included in Item 13 of sNDA 20-978.

August 3, 1999
Date

Karen L. Prus
Karen L. Prus, Ph.D.
Registered Patent Attorney
Registration No. 39,337

FINANCIAL DISLCOSURE AS TO CLINICAL INVESTIGATORS

Supplemental NDA 20-977: ZIAGEN® (abacavir sulfate) Tablets

Supplemental NDA 20-978: ZIAGEN® (abacavir sulfate) Oral Solution

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 *FR* 5233), as subsequently revised by publication on December 31, 1998 (63 *FR* 72171) (hereafter collectively referred to as the "rule"), financial interest information is provided for clinical investigators participating in studies covered by the rule included in these supplemental New Drug Applications 20-977 and 20-978 for Ziagen (abacavir sulfate) Tablets and Ziagen (abacavir sulfate) Oral Solution, respectively, indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. The following synopsis includes a description of methods used for the collection and reporting of the investigator financial disclosure information. Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and Forms FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) and supporting tables can be found in Item 19 (Vol. 36, Page 1).

The following is the "covered clinical study" for purposes of the rule for which Glaxo Wellcome was the sponsor:

PROTOCOL NO.	PROTOCOL TITLE	STUDY START DATE	STUDY STOP DATE
CNAA/B3005	A Phase III Randomized, Double-Blind, Multicenter Study to Evaluate the Safety and Efficacy of 3TC/ZDV/1592U89 and 3TC/ZDV/IDC in HIV-1 Infected Antiretroviral Therapy Naïve Subjects	21 OCT 97	08 JUN 99

Note: To arrive at the above-noted study "start" and "stop" dates, Glaxo Wellcome has defined the duration of the clinical study as the time period beginning with the first patient entered into the clinical study until the last patient assessment at the last site for the 48 week evaluation milestone. The protocol was amended April 1999 to extend the study to 96 weeks. As each subject completes 96 weeks of treatment, the investigator and subject is unblinded to treatment assignment. It is estimated that the study will complete in mid 2000.

Note: Protocol CNAA1012 is a Phase I Clinical Pharmacology study. This study is not a bioequivalence study. Accordingly, it does not fall within the definition of a "covered clinical study."

The rule specifies four categories of potentially disclosable financial interests. The approach taken to each is addressed below.

- **Compensation potentially affected by the outcome of the covered study [21 CFR 54.4(a)(3)(i), 54.2(a)]**

Glaxo Wellcome does not compensate clinical investigators in such a way as the total amount could vary with the outcome of the study. This is now formally stated in an organization-wide policy statement. Consequently, there are no disclosures in this category.

- **Significant payments of other sorts from the sponsor of the covered study [21 CFR 54.4(a)(3)(ii), 54.2(f)]**

Glaxo Wellcome relied upon financial data available internally to determine if the \$25,000 threshold was exceeded in the case of any individual clinical investigator. Consistent with the December 31, 1998 revisions to the rule, only payments made on or after February 2, 1999 were tracked. In addition, Glaxo Wellcome imposed a US and Rest of World (RoW) payment cut-off date of 31 August 1999 to allow sufficient time (roughly 90 days in advance of the submission date) for "other" payment information to be extracted from financial systems, compiled, and otherwise made "application-ready". Glaxo Wellcome has treated reimbursements of out-of-pocket expenses (such as travel costs incurred in the course of performing compensated services) as outside the definition of "payments of other sorts."

Based on available financial data, the \$25,000 threshold for "payments of other sorts" (between February 2, 1999 and the above referenced cut-off dates) was exceeded in the case of one principal investigator, _____ in _____ and five of his subinvestigators. The subinvestigators were _____

With regard to this site and associated investigators, a by-site analysis was conducted and specific statements are made as follows:

CNAA/B3005 was designed to assess efficacy, safety and tolerance of abacavir/Combivir (ABC/3TC/ZDV) versus indinavir/Combivir (IDV/3TC/ZDV) in antiretroviral naïve HIV-1 infected adults. The study was powered to demonstrate equivalence between the two treatment groups as measured by the proportion of patients with plasma HIV-1 RNA ≤ 400 copies/mL at 48 weeks, using the Roche Amplicor assay (limit of quantification 400 copies/mL). Subjects were stratified based on entry plasma HIV-1 RNA as follows: $\geq 10,000$ to 100,000 copies/mL and $> 100,000$ copies/mL. A total of 562 subjects were enrolled into this randomized double blind study between August 1997 and June 1998. Seventy-five study centers contributed subjects to the study.

The primary analysis was intention to treat (ITT) where subjects with missing data were considered treatment failures. In this analysis, almost half of the subjects in both treatment groups had plasma HIV-1 RNA concentrations ≤ 400 copies/ml at Week 48: 133/282 (47%) ABC/3TC/ZDV vs. 136/280 (49%) IDV/3TC/ZDV. The 95% confidence interval of the difference in proportions was (-10%, 7%). As this interval excludes the predefined equivalence limits of $\pm 12\%$, these results demonstrate equivalence between treatment groups.

This center enrolled 9 (1.6%) of 562 study subjects. Excluding all subjects from this site from the primary efficacy analysis results in a very similar outcome. The percentages of subjects with plasma HIV-1 RNA concentrations ≤ 400 copies/ml at Week 48 were 131/278 (47%) ABC/3TC/ZDV vs. 132/275 (48%) IDV/3TC/ZDV.

In summary, the contribution of this study center to the overall subject population was minor and, therefore, their ability to have a meaningful impact on the overall study outcome was not significant. As shown above, exclusion of these study subjects from the primary efficacy analysis did not alter interpretation of the study result.

It is not Glaxo Wellcome's practice to seek, or to maintain on file, the names of clinical investigators' spouses and dependent children, which would be necessary were searches to be conducted for "other" payments relative to those names. In this regard, please be advised that Glaxo Wellcome will not agree to compensate clinical investigators by making payments to their spouses or dependent children. This is now formally stated in an organization-wide policy statement.

- **Proprietary interest in the tested product (21 CFR 54.4(a)(3)(iii), 54.2(c))**

Relying on information available internally, Glaxo Wellcome has determined that no clinical investigator participating in the "covered study" has a proprietary interest in either ZIAGEN® (abacavir sulfate) Tablets or ZIAGEN® (abacavir sulfate) Oral Solution.

- **Significant equity interest in the sponsor of the covered study product (21 CFR 54.4(a)(3)(iv), 54.2(b))**

Relying on information obtained from the clinical investigators, Glaxo Wellcome has determined that one clinical investigator, _____, participating in Protocol CNAAB3005 has indicated that he holds a significant equity interest in Glaxo Wellcome. Specific information is located in Item 19 (Vol. 36, Page 34) of this application.

_____ participated as one of 11 subinvestigators for .
_____ enrolled 13 (2.31%) study subjects. The contribution of this study center to the overall subject population was minor and, therefore, the ability of one subinvestigator to have a meaningful impact on the overall study outcome was not significant.

Please note that information as to equity interest could not be obtained by written or verbal communications for one subinvestigator in the US, who did not comply with Glaxo Wellcome's request to provide equity information in a timely fashion to allow for inclusion in this submission, and 25 subinvestigators and one investigator at 13 different sites in Europe who did not respond. Specific information is located in Item 19 (Vol. 36, Page 34) of this application.

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDAs # 20-977 and 20-978

SUPPL# S-002

Trade Name: Ziagen™ Tablets and Oral Solution

Generic Name: abacavir sulfate

Applicant Name: Glaxo Wellcome Inc.

HFD # 530

Approval Date If Known: _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / **NO** / X /

b) Is it an effectiveness supplement?

YES / X / **NO** / /

If yes, what type? (SE1, SE2, etc.) SE8

This supplement contained a drug interaction study and 48 week data that was added to the clinical trials section of the label.

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / **NO** / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / /

NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / X / Granted 12/14/98

NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES / X /

NO / /

If yes, NDA # 20-977 and 20-978. Drug Name: Ziagen (abacavir) Tablets and Oral Solution.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / /

NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)**

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/

NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/

NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?

(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / ☐ / NO / ☐ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?**

YES / ☐ / NO / ☐ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / ___ /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ /

NO / ___ /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ___ /

NO / ___ /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or

sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES / ___ / NO / ___ / Explain: _____

Investigation #2

IND # _____ YES / ___ / NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

Investigation #2

YES / ___ / Explain _____ NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the

drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

/S/

Signature of Project Manager:

10-16-00
Date

/S/

Signature of Division Director

10/17/00
Date

cc: Original NDA
HFD-530/Division File
HFD-530/PM/Truffa
HFD-93 Mary Ann Holovac
HFD-104/PEDS/T. Crescenzi

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 020977 **Trade Name:** ZIAGEN (ABACAVIR SULFATE) TABLETS
Supplement Number: 002 **Generic Name:** ABACAVIR SULFATE TABLETS
Supplement Type: SE8 **Dosage Form:**
Regulatory Action: OP **COMIS Indication:** TREATMENT OF HIV INFECTION
Action Date: 12/17/99

Indication # 1 Ziagen, in combination with other antiretroviral agents, is indicated for the for the treatment of HIV-1 infection.

Label Adequacy: Adequate for ALL pediatric age groups

Formulation Needed NO NEW FORMULATION is needed

Comments (if any): 10/25/00: Ziagen (abacavir sulfate) Tablets and oral solution are labeled for use in pediatric patients age 3 months to 16 years. Additional studies in patients 0 to 3 months of age have been waived because of the potential for serious hypersensitivity reactions in this patient population. Pediatric exclusivity was granted 12/14/98.

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
3 months	Adult	Completed	12/17/98
0 months	3 months	Waived	12/17/98

Comments: Additional studies in patients 0-3 months have been waived for safety reasons (serious and/or fatal hypersensitivity reactions).

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Signature -

Date

10-25-00

**REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROLS
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)**

1. CHEMISTRY REVIEW #: 2

2. IND #: 20,977

3. NAME & ADDRESS OF APPLICANT: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

4. SUPPLEMENT(S)#: Document #SE-8, Sequence #002

5. PROPRIETARY NAME: ZIAGEN®

6. NONPROPRIETARY NAME: Abacavir Sulfate

7. CODE NAME: 1592U89 Hemisulfate

8. CHEM TYPE/SUBMISSION PRIORITY: N/A

9. SUPPLEMENT(S) PROVIDE(S) FOR: a request to include the results of CNAAB3005 (a 48-week study comparing abacavir sulfate plus Combivir versus Indinavir plus Combivir) and CNA1012 (the methadone/abacavir interaction study) studies in the package insert for Ziagen (abacavir sulfate) tablets.

<u>10. PREVIOUS DOUMENTS</u>	<u>DOCUMENT DATE</u>
N/A	N/A

<u>11. SUBMISSION(S) REVIEWED</u>	<u>DOCUMENT DATE</u>
Supplement SE8/002	12-16-99

12. PHARMACOLOGICAL CATEGORY: Antiviral

13. Rx or OTC: Rx

14. DOSAGE FORM: Tablet

15. STRENGTH/POTENCY: 300 mg of abacavir as abacavir sulfate/capsule

16. ROUTE OF ADMINISTRATION: Oral

17. SPOTS: ☒ No ☐ Yes

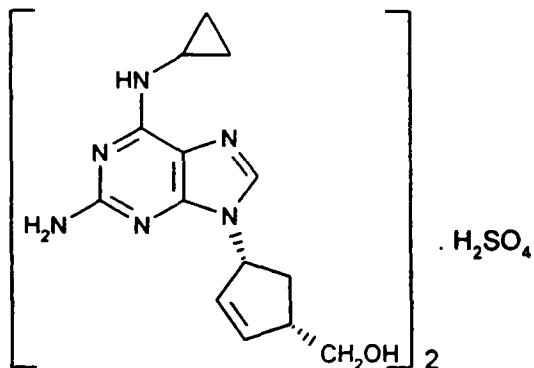
**18. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:**

Chemical Name: CAS: (1*S*, *cis*)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-

yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)

IUPAC: [4*R*-(2-Amino-6-cyclopropylamino-purin-9-yl)-cyclopent-2-en-1*S*-yl]-methanol sulfate (2:1)

Structural Formula:



Molecular Formula:

(C₁₄H₁₈N₆O)₂ . H₂SO₄

Molecular Weight:

670.76

Chirality/Stereochemistry:

abacavir sulfate is a single enantiomer with 1*S*, 4*R* configuration.

19. **RELATED/SUPPORTING DOCUMENTS:** IND# 45,331 (abacavir sulfate tablets and oral solution) and NDA #20-977 (abacavir sulfate tablets; Glaxo Wellcome)

20. **STATUS OF CONSULTS AND OTHER REVIEWS:** N/A

21. **REMARKS/COMMENTS:**

The NDA#20-977 for Ziagen tablets was approved by the FDA on 12/17/98. The purpose of this Supplemental Application is to include the results of CNAAB3005 (a 48-week study comparing abacavir sulfate plus Combivir versus Indinavir plus Combivir) and CNAA1012 (the methadone/abacavir interaction study) studies in the package insert for Ziagen tablets. The Applicant did not propose any changes to the currently approved CMC for Ziagen tablets. Also, no changes were proposed to the chemistry related information in the currently approved package insert.

22. CONCLUSIONS & RECOMMENDATIONS:

From the CMC stand point the efficacy supplement SE8/002 to the NDA #20-977 is recommended for approval.

23. REVIEWER

151

DATE COMPLETED 7/18/00

Kao V. Kambhampati, Ph.D.
Senior Regulatory Review Scientist

Concurrence:

HFD-530/Chem. TL/SMille

151

cc:

Orig. IND #20-977

HFD-530/Chem TL/SMiller

HFD-530/PM/MTruffa

HFD-530/Micro/LMishra

HFD-530/Chem/RKambhampati

HFD-530/MO/Iibia

HFD-530/Pharm/PVerma

24. LIST OF DEFICIENCIES AND COMMENTS: N/A

Statistical Review

NDA#:	20-977
APPLICANT:	Glaxo Wellcome
NAME OF DRUG:	Ziagen (Abacavir)
INDICATION:	Anti-HIV
Clinical Reviewer:	Ekopimo Ibia, MD
Statistical Reviewer:	Andrei Breazna, Ph.D.

1. Introduction

The submission contains one Phase III randomized, double-blind study (CNAAB3005) that evaluates the efficacy and safety of 3TC/ZDV/ABC and 3TC/ZDV/IDV in HIV-1 infected antiretroviral therapy naïve subjects. The study was conducted in clinical centers in North America, Europe, and Australia. Subjects were equally randomized to the two treatment groups, stratified by the screening plasma HIV-1 RNA (Stratum 1 for $10000 \leq \text{HIV-1 RNA} \leq 100000$ and Stratum 2 for $\text{HIV-1 RNA} > 100000$).

Enrolled subjects were scheduled for visits at weeks 2, 4, and every four weeks thereafter till 48 weeks. The original protocol had for the primary efficacy analysis the equivalence of proportions of patients who achieved plasma HIV-1 RNA < 400 copies/mL at week 48. However, the same protocol encouraged the clinicians to take measures if the patient has viral rebound (viral load has two consecutive readings above the limit of quantification of 400 after he/she achieves viral load below 400 copies/mL). The impact of viral rebounds prior to week 48, AIDS defining events and therapy switches (any changes in the ART) on the primary analysis is not clearly pre-specified.

A secondary analysis with the ultra sensitive assay (less than 50 copies/mL) is also provided. The strata adjustment has no contribution.

Since the study's goal is to demonstrate the equivalence of the two treatment arms, 95% confidence intervals (normal approximation with continuity correction) of the difference in failure rates (Abacavir-Indinavir) will be provided. In order to prove non-inferiority, the upper bound of the confidence interval has to be less than 10%-12%. Since we believe that the contribution of the competitor drug (Indinavir) to the combination is much larger than 12%, we are sure that this claim for equivalence between Abacavir and Indinavir implies also superiority to a hypothetical placebo. We will compare the results obtained with and without adjusting for the randomization strata. A discussion of the appropriateness of strata-adjustment will also be included.

Throughout the review, unless otherwise noted, we define viral suppression as the occurrence of a measurement of less than 400 copies of HIV RNA1 per mL (the lower detection limit for the Roche standard assay).

This review will concentrate on the Week 48 data analysis. The datasets originally submitted did not include clear information about the past viral rebounds, AIDS defining events, protocol violations, withdrawn consents or changes of therapy. Upon the reviewer's request the sponsor provided a dataset that contained the missing information. The FDA statistical reviewer treated the past viral rebounds, AIDS defining events, discontinuations, and treatment switches as failures, even if the patient had a low viral load at week 48. This is in line with the current labeling and regulatory practice for this therapeutic area. This analysis could not reproduce/confirm the sponsor's numerical findings. We understand that most of the discrepancies are due to the fact that the sponsor allowed subjects with early viral rebound (defined as two consecutive visits with HIV-1 RNA count above 400 copies/mL after the patient achieved viral suppression.) to be considered successes at 48 weeks (if their status at that time was of viral suppression). It is apparent that some of the sponsor's analyses presented to the FDA or in professional meetings (Interscience Conference of Antimicrobial Agents and Chemotherapy, Sept 26-29, 1999) did not consider as treatment failures a number of patients that experienced AIDS defining events, changes in ART, or were lost to follow-up, withdrew their consent or had missing data for other reasons. Our analysis is on the Intent-To-Treat population- which includes patients that took at least one dose of the study drug. Of the 562 subjects randomized, 20 in the Abacavir arm and 15 in the Indinavir arm did not initiate treatment, so a total of 527 will be included in the ITT population.

Note that in this review the numbers presented differ from the numbers in the label due to two reasons. First, failure rates are used in this review while success rates are used in the label; second, the analyses in this review is based on all subjects randomized who took at least one dose of study medication while in the label all subjects randomized are used as the denominator. None of these differences had an impact on the efficacy conclusions.

2. Demographics

The distribution of age, baseline CD4 count, and baseline HIV1-RNA count appear to be balanced between the two treatment arms. The gender and racial makeup of the treatment arms do not appear to differ. The tables 1-3 contain the detailed information about the demographics of the ITT population.

Table 1

	Treatment	Number	Mean	Std Dev	Median
Age	ABC	262	36.79	9.73	35
	IDV	265	37.06	9.33	36
Baseline CD4 count	ABC	259	377.7	163.28	352
	IDV	260	383.88	188.62	357.5
Baseline Log ₁₀ PCR	ABC	260	4.88	0.51	4.9
	IDV	263	4.82	0.47	4.8

Table 2 Distribution of Race by treatment arm (ITT population)

	ABC/3TC/ZDV	IDV/3TC/ZDV	Total
American Hispanic	20 (7.72 %)	26 (9.85 %)	46 (8.79 %)
Asian	3 (1.16 %)	5 (1.89 %)	8 (1.52 %)
Black	44 (16.99 %)	32 (12.12 %)	76 (14.53 %)
Other	2 (0.77 %)	3 (1.14 %)	5 (0.95 %)
White	190 (73.36 %)	198 (75.00 %)	388 (74.18 %)
Total	259	264	523

Table 3 Distribution of gender by treatment arm

	ABC	IDV	Total
Female	31 (11.83%)	35 (13.21%)	66 (12.52 %)
Male	231 (88.17%)	230 (86.79%)	461 (87.47 %)
Total	262	265	527

3. Adverse events

Tables of adverse events (if over 5% in one arm), serious adverse events and concomitant medication (if over 5% in one arm) are annexed in Appendix 1. We summarize the reporting of adverse events by saying that:

- 94.7%, or 248 patients in the ABC/3TC/ZDV arm reported adverse events vs. 96.2%, or 255 patients in the IDV/3TC/ZDV arm.
- 8.4%, or 22 patients in the ABC/3TC/ZDV arm reported hypersensitivity vs. 7.2%, or 19 patients in the IDV/3TC/ZDV arm.
- 16.8%, or 44 patients in the ABC/3TC/ZDV arm withdrew because of an adverse event vs. 21.5%, or 57 patients in the IDV/3TC/ZDV arm.
- 21%, or 55 patients in the ABC/3TC/ZDV arm reported serious adverse events vs. 22.2%, or 59 patients in the IDV/3TC/ZDV arm.
- 13.8%, or 34 patients in the ABC/3TC/ZDV arm reported severe adverse events vs. 16.6%, or 44 patients in the IDV/3TC/ZDV arm.

We did not see any remarkable imbalance in the number of patients reporting adverse events between the treatment arms.

4. Efficacy

For the primary endpoint defined by the FDA, failures could be due to reasons other than virologic rebound, like discontinuations due to adverse events, CDC Class C events, early withdrawals etc., Tables below summarize the reasons for failure by treatment (Table 4) and further by randomization strata (Table 5).

Table 4 Reasons of failure by treatment arm at week 48 (one per patient).

Reason	ABC N=262	IDV N=265	TOTAL N=527
Responders (non-failures)	129 (49.23%)	132 (49.81%)	261 (49.52%)
Adverse Event	25 (9.54%)	32 (12.07%)	57 (10.81%)
CDC Class C	5 (1.9%)	1 (0.37%)	6 (1.13%)
Changed ART*	3 (1.14%)	3 (1.13%)	6 (1.13%)
Confirmed Failure**	43 (16.41%)	40 (15.09%)	83 (15.74%)
Consent Withdrawn	2 (0.76%)	3 (1.13%)	5 (0.94%)
Lost to Follow Up	6 (2.29%)	5 (1.88%)	11 (2.08%)
Met Protocol Defined Switch Crit.	2 (0.76%)	3 (1.13%)	5 (0.94%)
Never Below 400 Copies/ml	35 (13.35%)	31 (11.69%)	66 (12.52%)
No RNA Sample	5 (1.9%)	7 (2.64%)	12 (2.27%)
Other	6 (2.29%)	5 (1.88%)	11 (2.08%)
Protocol Violation	1 (0.38%)	3 (1.13%)	4 (0.75%)
Total failures (responders excluded)	133 (50.76%)	133 (50.18%)	266 (50.47%)

* Adding or switching of any drug in the randomized regimen

** two consecutive measurements >400 copies/mL after achieving <400 copies/mL for HIV RNA level

Table 5 Reasons of failure by strata and treatment arm at week 48 (one per patient).

Reason	Strata 1 (331 subjects)		Strata 2 (195 subjects)	
	ABC (166)	IDV (165)	ABC (96)	IDV (99)
Responders (non-failures)	83 (50%)	80 (48.48%)	46 (47.91%)	52 (52.52%)
Adverse Event	21 (12.65%)	26 (15.75%)	4 (4.16%)	6 (6.06%)
CDC Class C	2 (1.2%)	1 (0.6%)	3 (3.12%)	0 (0%)
Changed ART*	3 (1.8%)	3 (1.81%)	0 (0%)	0 (0%)
Confirmed Failure**	26 (15.66%)	22 (13.33%)	17 (17.7%)	18 (18.18%)
Consent Withdrawn	0 (0%)	3 (1.81%)	2 (2.08%)	0 (0%)
Lost to Follow Up	6 (3.61%)	4 (2.42%)	0 (0%)	1 (1.1%)
Met Protocol Defined Switch Criterion	0 (0%)	2 (1.21%)	2 (2.08%)	1 (1.1%)
Never Below 400 Copies/mL	15 (9.03%)	16 (9.69%)	20 (20.83%)	15 (15.15%)
No RNA Sample	4 (2.4%)	4 (2.42%)	1 (1.04%)	2 (2.2%)
Other	5 (3.01%)	2 (1.21%)	1 (1.04%)	3 (3.3%)
Protocol Violation	1 (0.6%)	2 (1.21%)	0 (0%)	1 (1.1%)

* Adding or switching of any drug in the randomized regimen

** two consecutive measurements >400 copies/mL after achieving <400 copies/mL for HIV RNA level

Note that the two strata have numerically different rates of failures due to adverse events and of subjects never below 400 copies/mL. The treatment arms overall and within strata present similar rates for reason of failure.

Table 6 gives the equivalence analyses results using the Roche Amplicor assay. Note the failures are determined using the FDA definition with all AIDS-defining events, viral rebounds before Week 48, and treatment switches as failures.

Table 6 Failure rates by week 48 in different sub-populations.

Cohort		Failure rate ABC	Failure rate IDV	Difference (ABC-IDV)	95%, Confidence Interval of Difference*
ALL		133/262=50.76%	133/265=50.18%	0.57%	(-8%,9.49%)
USA ¹		63/121=52.06%	69/120=57.50%	-5.43%	(-18%,7.94%)
Non-US		69/140=49.28%	63/142=44.36%	4.91%	(-7%,17.26%)
Strat1 ²		83/166=50.00%	85/165=51.51%	-1.51%	(-12%,9%)
Strat2 ²		50/96=52.08%	47/99=47.47%	4.60%	(-10%,19%)
Baseline HIV RNA	Missing	1/2=50.00%	2/3=66.66%	16.66%	NA
	≤4	14/10=40.00%	3/9=33.33%	6.66%	(-47%,60%)
	4-4.5	25/52=48.07%	33/63=52.38%	-4.30%	(-24%,15%)
	4.5-5	25/94=47.87%	34/96=56.25%	-8.37%	(-23%,6%)
	5-5.5	31/92=33.70%	35/74=47.29%	-13.59%	(-29%,2%)
	≥5.5	19/33=57.57%	16/20=80.00%	-22.42%	(-52%,5%)

¹ US vs. Non-US sites.

² Based on HIV RNA count at screening. Confidence intervals may be widened by the small sample size.³ Collapsed baseline Log₁₀ HIV RNA. Confidence intervals may be widened by the small sample size.

* Results obtained with the ultra-sensitive assay (responders have less than 50 HIV RNA copies/mL)

* Normal approximation with continuity correction; strata adjustment has no visible impact.

The reviewer's results confirm the sponsor's analysis for the ITT-exposed to study drug population. Table 7 summarizes the sponsor's findings for the protocol defined ITT and for the ITT-Exposed to study drug populations/Missing=Failure. The protocol defined ITT population contains a number of subjects that were considered successes at week 48, even if they had different types of virological failures or AIDS defining events during the trial. This is in sharp discordance with the current labeling practices, especially for reporting the failure (or responder) rates. The confidence intervals for the rate of failure in the protocol defined ITT population is very similar to the one found in the ITT-Exposed to study drug populations/Missing=Failure.

Table 7 Failure rates, G-W analysis

Population	ABC	IDV	95%, Confidence Interval of Difference*
ITT protocol defined	116/282=41.13%	116/280=41.42%	(-8%,8%)
ITT Exposed/ Missing=Failure	129/262=49.23%	129/265=48.67%	(-8%,9%)

* Normal approximation with continuity correction; strata adjustment has no visible impact.

Table 8 summarizes the sponsor's analysis for the ultra-sensitive assay vs. the FDA reviewer's analysis.

Table 8 Failure rates ITT, Exposed/Missing=Failure

Population	ABC	IDV	95%, Confidence Interval of Difference ^a
ITT FDA	157/262=59.92%	145/265=54.71%	(-3%,14%)
Str1 FDA	93/166=56.02%	88/165=53.33%	(-8%,13%)
Str2 FDA	64/96=66.67%	56/99=56.57%	(-3%,23%)
ITT G-W	158/262=60.30%	144/265=54.33%	(-2%,14%)
Stra1 G-W	92/166=55.42%	89/165=53.93%	(-8%,13%)
Stra2 G-W	66/90=68.75%	55/100=55%	(-4%,23%)

^aNormal approximation with continuity correction; strata adjustment has no visible impact.

Note that in both analyses the ultra-sensitive test yields a difference of more than 5% in failure rates, making Abacavir numerically inferior to Indinavir, with a confidence interval for the difference whose right-hand side goes over 14%. The FDA reviewer used the information from the standard assay to replace the missing data from the ultra-sensitive assay; all failures under the standard assay are considered failures under the ultra-sensitive analysis.

Figure 1 and 2 below show the relationship between the baseline viral load and Week 48 failure rates. Failure rates in the Table 6 above for the five categories defined by baseline Log₁₀ HIV RNA are plotted in the Figure 1. While it is easy to accept the linear (increasing) shape of Abacavir's failure rates vs. baseline Log₁₀ of viral load, we see no obvious explanation for the parabolic shape of the failure rates in the Indinavir. The breakdown by randomization strata has the same features (see Table 6 and Figure 2).

Figure1: Failure rates at the 48th week by collapsed baseline Log₁₀ viral load.

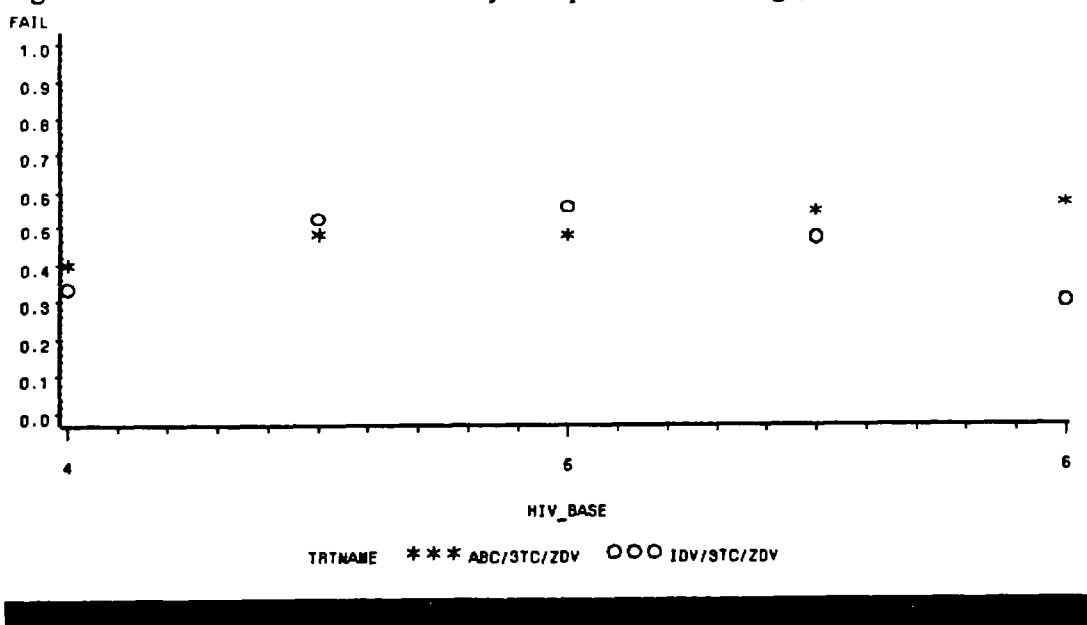
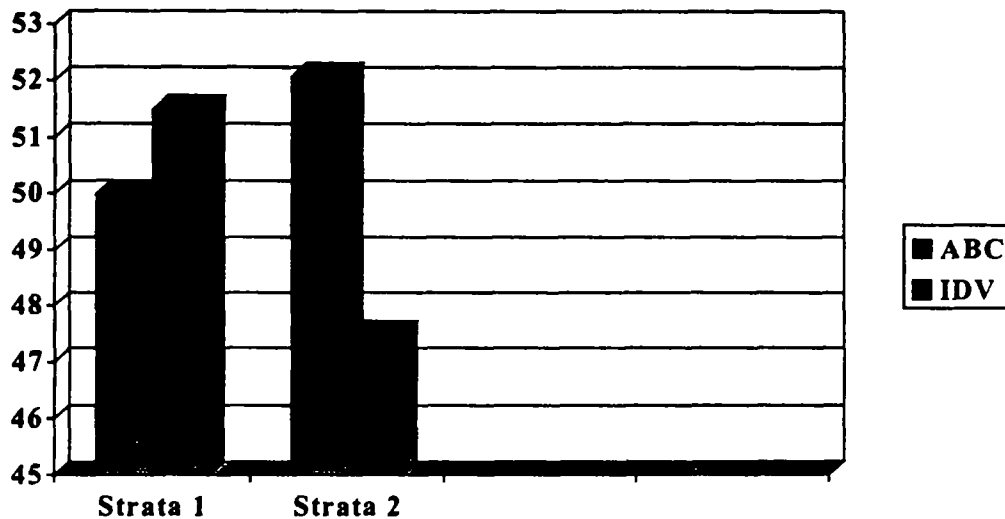


Figure 2

Failure Rates by Strata and Treatment Arm

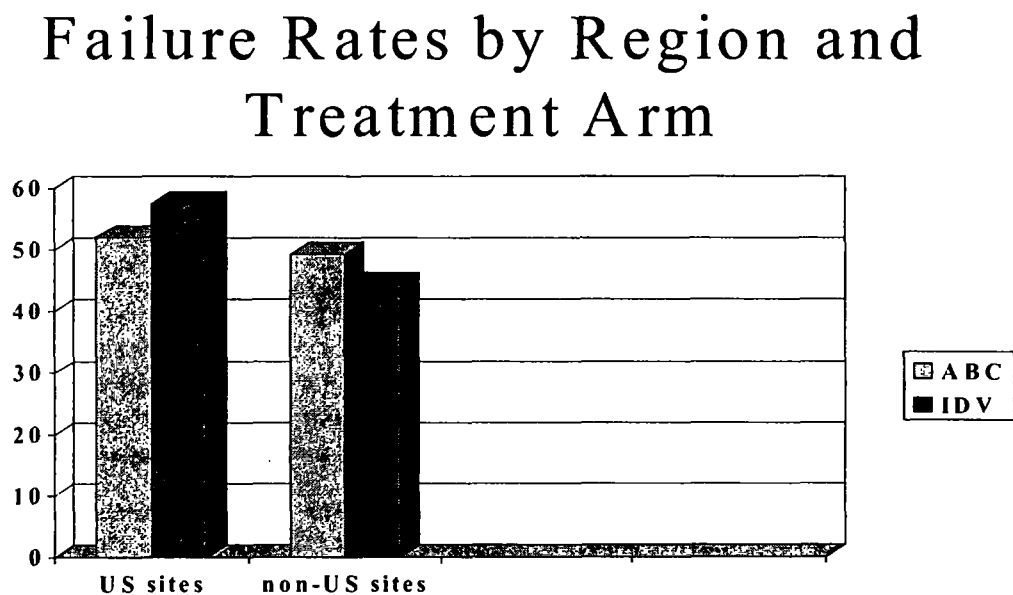


The difference of treatment differences in Figure 2 is not statistically significant, but the opposite trends are still hard to understand. The 95% confidence interval for the difference of treatment differences ($ABC \text{ Strata1} - IDV \text{ Strata1} - ABC \text{ Strata2} + IDV \text{ Strata2}$) is $(-17\%, 17\%)$. The opposite trends may be due to chance, or this may indicate some irregularities in the process of data collection or in the way the trial was conducted. There is no intuitive explanation for Indinavir having a lower failure rate at higher baseline viral loads.

Figure 3 plots the failure rates by region (US vs. non-US sites) and by treatment. We see the failure rates are lower in the non-US sites for both treatment arms. However, this difference is larger for the indinavir arm and it is statistically significant ($p\text{-value}=0.036$ by Fisher's Exact Test) at significance level 0.05. To test if the treatment effects are homogeneous by region, we test if the difference of the treatment differences

in the two regions are statistically significantly different from 0. This test leads to a p-value of 0.07. Considering that typically we will do subgroup analyses by age, gender, race in addition to the randomization strata and region, multiple adjustment for this p-value using Bonferoni approximation yields p-value of $0.07 \times 5 = 0.35$. Therefore we cannot rule out that the apparent numerical differences in treatment effects in the two regions may be due to chance. To ascertain this claim, future trials with one or two of the treatment arms in this trial need to be examined.

Figure 3



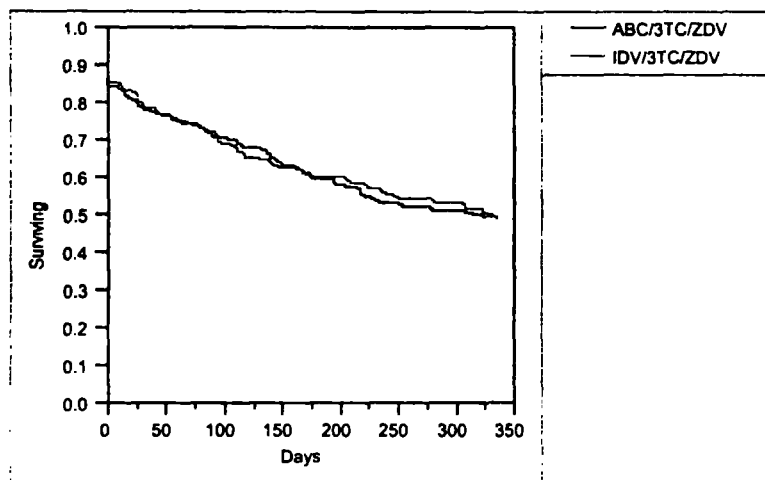
The troubling fact that Indinavir appears to be less effective in the US is hard to ignore, but we can give no reasonable explanation. In Table 9 we track down possible interactions between the region (US vs. non-US) and stratum. Different medical standards of patient management may be responsible for the fact that The Indinavir arm has a lot of variability within Strata and between Regions.

Table 9 Failure rates by Region, Treatment arm and Strata

Region	Treatment	Failure rates Strata1	Failure rates Strata2
Non-US	ABC	40 / 89 = 45 %	29 / 51 = 57 %
	IDV	40 / 91 = 44 %	23 / 51 = 45 %
US	ABC	42 / 76 = 55 %	21 / 45 = 47 %
	IDV	45 / 73 = 62 %	23 / 46 = 50 %

The survival curves corresponding to the two treatment arms are virtually indistinguishable.

Figure 4



According to Table 4, the proportions of subjects lost to follow-up, no RNA values and “other” in the treatment arms are similar, so an alternate analysis of the reasons for failure would yield the same conclusions.

5. Secondary Efficacy

This section will deal primarily with the CD4 count. Given the shape of the submitted data, we’ll summarize the CD4 count for patients that were still responders during the 48th week of the trial. Since the failure rates are similar, the comparison of the 48th week responders does not have a major bias.

Table 10

Nonparametric tests performed on the different measures of CD4 count confirmed a conclusion of equivalence.

Table 10 CD4 count statistics

	ABC Mean (SD)[Median]	IDV Mean (SD)[Median]	Difference Of Means (ABC-IDV)	Difference Of Medians (ABC-IDV)
Baseline CD4	386 (159) [375]	380 (195) [337]	6	38
48week CD4	588 (248) [571]	580 (225) [567]	8	4
48week CD4-Baseline	189 (139) [171]	199 (151) [191]	-10	-20

Using and validating the sponsor's programs that allowed for analysis of the data with last observation carried forward, we did confirm the claim that the CD4+ cell count median change from baseline at Week 48 were comparable between the two arms (152 ± 10.52 cells/mm³ for the abacavir group (N=204) and 149 ± 10.23 cells/mm³ for the indinavir group (N=220)). We recommend that the label contain a statement that the CD4+ cell count median change from baseline at Week 48 was approx. 150 in both arms.

6. Conclusions

The confidence interval of the difference in failure rates (ABC-IDV) is (-8%,9%), therefore the upper limit is less than the non-inferiority margin of 10~12%. However there are possible challenges to the claim of efficacy. They stem from the unusual behavior of the reference arm (Indinavir). The differences between the US and non-US sites of this arm, as well as the apparent improved efficacy of Indinavir at high (Strata2 i.e. HIV-1 RNA>100000) baseline viral loads vs. low (Strata1 i.e. $10000 \leq$ HIV-1 RNA ≤ 100000) viral loads have a potential for invalidating the study.

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HFD-725/StatTL/GSoon
HFD-725/Stat/ABreazna
HFD-725/StatDivDir/MHuque
HFD-725/StatSec/DRobinette

Appendix

Adverse events (if more than 5% in one treatment arm)

MIDAS coded adverse event	No. patients ABC (262 patients)	Percentage ABC	No. patients IDV (265 patients)	Percentage IDV
Abdominal discomfort & pain	35	13.35878	43	16.22642
Abdominal distension	28	10.68702	16	6.037736
Abnormal enzyme levels	17	6.48855	19	7.169811
Abnormal liver function tests	19	7.251908	16	6.037736
Acne & folliculitis	14	5.343511	7	2.641509
Anxiety	24	9.160305	19	7.169811
Arthralgia & articular rheumatism	21	8.015267	18	6.792453
Breathing disorders	18	6.870229	7	2.641509
Bronchitis	10	3.816794	22	8.301887
Chest symptoms	17	6.48855	9	3.396226
Constipation	22	8.396947	17	6.415094
Cough	44	16.79389	35	13.20755
Decreased white cells	14	5.343511	15	5.660377
Depressive disorders	27	10.30534	23	8.679245
Diarrhea	69	26.33588	73	27.54717
Disorders of sweat & sebum	25	9.541985	68	25.66038
Dizziness	19	7.251908	36	13.58491
Dyspeptic symptoms	18	6.870229	18	6.792453
Dysuria	4	1.526718	18	6.792453
Ear nose & throat infection	29	11.0687	33	12.45283
Feeding problems	39	14.8855	29	10.9434
Fungal skin infection	18	6.870229	19	7.169811
Gaseous symptoms	25	9.541985	28	10.56604
Gastrointestinal discomfort & pain	18	6.870229	17	6.415094
Headache	74	28.24427	67	25.28302
Hyposalivation	4	1.526718	28	10.56604
Lymphatic signs & symptoms	15	5.725191	11	4.150943
Malaise & fatigue	118	45.03817	111	41.88679
Muscle pain	23	8.778626	21	7.924528
Musculoskeletal pain	42	16.03053	45	16.98113
Nasal inflammation	8	3.053435	16	6.037736
Nasal signs & symptoms	32	12.21374	25	9.433962
Nausea	159	60.68702	160	60.37736
Nausea & vomiting	79	30.15267	73	27.54717
Oral ulceration	5	1.908397	14	5.283019
Pain	16	6.10687	20	7.54717
Pruritus	23	8.778626	40	15.09434
Renal signs & symptoms	2	0.763359	16	6.037736
Skin rashes	27	10.30534	45	16.98113
Sleep disorders	34	12.9771	34	12.83019
Sweating	27	10.30534	24	9.056604
Taste impairment	6	2.290076	22	8.301887
Temperature regulation disturbance	53	20.22901	36	13.58491
Throat & tonsil discomfort & pain	28	10.68702	29	10.9434

Upper respiratory inflammation	11	4.198473	14	5.283019
Viral ear nose & throat infection	22	8.396947	24	9.056604
Viral infection	10	3.816794	17	6.415094
Viral respiratory infection	36	13.74046	36	13.58491
Viral skin infection	8	3.053435	23	8.679245

Serious Adverse Events (all)

Event	ABC	IDV
Abdominal discomfort & pain	1	2
Abnormal bilirubin levels	2	1
Abnormal enzyme levels	13	14
Abnormal liver function tests	11	7
Abnormal pancreatic enzymes	1	0
Alcohol use abuse & withdrawal	0	1
Allergy & allergic reaction	3	0
Anemia	0	3
Appendicitis	0	1
Arrhythmias	1	0
Blindness & low vision	0	1
Complications of medical care	1	0
Compressed nerve syndromes	0	1
Death	1	0
Decreased white cells	2	4
Depressive disorders	2	0
Diarrhea	2	1
Disorders of lipid metabolism	2	2
Disorders of sweat glands	1	0
Dizziness	1	0
Fracture	2	1
Gastritis	0	1
Gastroenteritis	1	1
Gastrointestinal hemorrhage	1	0
Gastrointestinal herniae	0	1
Headache	0	1
Hematological disorders	1	0
Hepatitis	0	1
Hepatocellular disorders	0	1
Infection	0	1
Lower respiratory failure	1	0
Lower respiratory infection	0	1
Lymphatic signs & symptoms	0	1
Malaise & fatigue	0	1
Male reproductive tract pain	1	0
Myocardial infarction	1	0
Nausea	4	1
Nausea & vomiting	3	0
Nephritis & nephrosis	1	0
Neuropathy	0	1
Oral erythema	1	0
Overdose	2	1
Pain	0	2

Paralysis of cranial nerves	0	1
Pneumonia	3	2
Primary malignant blood & lymphatic neoplasia	0	2
Primary malignant skin neoplasia	1	0
Primary malignant urinary neoplasia	0	1
Psychiatric procedures	2	0
Quantitative platelet defect	2	1
Renal signs & symptoms	0	7
Reproductive infection	0	1
Skin erosion & ulcers	1	0
Skin lesions	1	0
Skin rashes	5	2
Spirochete & actinomycete neurological infection	0	2
Suicide & attempted suicide	2	0
Swallowing disorders	1	0
Tachyarrhythmias	1	0
Temperature regulation disturbance	6	1
Urinary calculi	0	2
Urinary infection	0	2
Urinary tract obstructions	0	1
Urticaria	1	0
Viral eye infection	0	1
Viral gastrointestinal infection	0	1
Viral hepatobiliary & pancreatic infection	1	0
Wounds & lacerations	1	0

Concomitant medication (if more than 5% in one treatment arm)

Concomitant Medication	IDV		ABC	
	No. patients	% Patients	No. patients	% Patients
Fluticasone propionate	15	5.660377	5	1.908397
Cetirizine hydrochloride	17	6.415094	6	2.290076
Pseudoephedrine hydrochloride	9	3.396226	15	5.725191
Nelfinavir mesylate	16	6.037736	10	3.816794
Augmentin	11	4.150943	15	5.725191
Loperamide hydrochloride	14	5.283019	13	4.961832
Promethazine hydrochloride	17	6.415094	13	4.961832
Hydrocortisone	24	9.056604	8	3.053435
Clotrimazole	19	7.169811	13	4.961832
Metoclopramide hydrochloride	19	7.169811	13	4.961832
Azithromycin	19	7.169811	14	5.343511
Compazine	17	6.415094	16	6.10687
Diphenhydramine hydrochloride	17	6.415094	16	6.10687
Lamivudine	18	6.792453	16	6.10687
Ketoconazole	24	9.056604	14	5.343511
Ascorbic acid	22	8.301887	16	6.10687
Fluconazole	21	7.924528	17	6.48855

Stavudine	23	8.679245	20	7.633588
Influenza vaccine	22	8.301887	29	11.0687
Acyclovir	34	12.83019	18	6.870229
Aspirin	27	10.18868	25	9.541985
Ibuprofen	31	11.69811	47	17.93893
Co-trimoxazole	49	18.49057	34	12.9771
Multivitamins	40	15.09434	47	17.93893
Paracetamol	46	17.35849	56	21.37405

/s/

Andrei Breazna
12/14/00 03:14:58 PM
BIOMETRICS

Greg Soon
12/14/00 03:28:27 PM
BIOMETRICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

REVIEWER : Prabhu Rajagopalan, Ph. D.
NDA : 20977_SE8002
APPLICANT : GlaxoWellcome
DRUG (STRENGTH) : Abacavir (300 mg)
SUBMISSION DATE : December 17, 1999
DRAFT REVIEW : May 30, 2000
FINAL REVIEW : July 20, 2000

BACKGROUND: Report of a study assessing the pharmacokinetic interaction between abacavir and methadone is the only report that has been submitted to Section 6 of this NDA supplement.

STUDY TITLE: A study to evaluate the pharmacokinetics of abacavir and methadone following co-administration (Protocol CNA1012).

OBJECTIVES: To determine the pharmacokinetic interaction when abacavir and methadone are administered concomitantly.

SUBJECTS: 11 HIV-infected subjects (10 males and 1 female) completed the 28-day study.

STUDY DESIGN: The following design was adopted.

Day 1 : Abacavir 600 mg
Days 2 – 28 : Methadone titrated to control withdrawal effects
Days 15 – 28 : Abacavir 600 mg BID.

All doses were administered after an 8-hour fasting period. The individual doses of methadone varied from 40 mg to 90 mg once daily.

Reviewer's remarks:

SAMPLE COLLECTION: Blood samples were collected at predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12 hours postdose on Days 1, 14, 15 and 28. Additional samples were collected 24 hours postdose on Days 14 and 28.

ANALYTICAL METHODOLOGY: Abacavir and methadone concentrations in plasma were determined using an HPLC method with UV detection using different methods. The performance of the analytical methods used in the analysis of plasma samples is shown below.

Analyte	QC concentration	n	Accuracy (% of nominal)	Precision (%CV)
Abacavir		16	99.4	5.1
		16	99.9	2.8
		16	102.9	2.7
Methadone		14	95.7	4.5
		14	94.6	4.3
		14	96.5	2.1

PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters were obtained by non-compartmental methods. Analysis of variance was performed with log transformed pharmacokinetic parameters. The point estimates and 90% confidence intervals were obtained following analysis of variance. Since subjects received varying doses of methadone, methadone CL/F was the primary pharmacokinetic parameter for statistical analysis.

Effect of methadone on abacavir

The mean plasma abacavir concentration-time profiles on Days 1, 15 and 28 are shown in Figure 1 and the pharmacokinetic parameters are summarized in Tables 1 and 2.

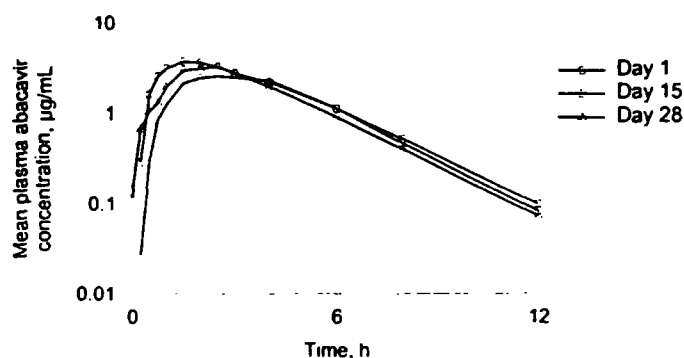


Figure 1

Table 1. Mean (%CV) pharmacokinetic parameters of abacavir on Days 1 and 15

PK parameter	Day 1 (n = 12)	Day 15 (n = 12)	Day 15 / Day 1 ratio [90% CI] *
C_{max} , µg/mL	4.65 (35)	3.10 (40)	0.65 [0.53 – 0.80]
AUC_{∞} , µg.h/mL	16.77 (72)	13.19 (45)	0.85 [0.70 – 1.04]
CL/F, L/h	47.42 (48)	53.33 (40)	1.18 [0.96 – 1.43]

Table 2. Mean (%CV) pharmacokinetic parameters of abacavir on Days 1 and 28

PK parameter	Day 1 (n = 11)	Day 28 (n = 11)	Day 28 / Day 1 ratio [90% CI] *
C_{max} , µg/mL	4.53 (37)	3.92 (41)	0.82 [0.60 – 1.12]
AUC_{∞} , µg.h/mL	16.56 (77)	13.89 (54) **	0.85 [0.60 – 1.21]
CL/F, L/h	48.88 (48)	63.35 (90)	1.17 [0.83 – 1.66]

* Ratios and 90% CI are based on geometric means ** AUC_{12}

Comparison of Day 1 abacavir pharmacokinetic data to either Day 15 data (first concomitant dose of abacavir) or Day 28 data (steady-state concomitant dose of abacavir) indicate that exposure to abacavir is decreased in the presence of methadone. Since anti-HIV medications are dosed chronically, it is acceptable to compare pharmacokinetic parameters observed on Day 1 with those observed on Day 28. As seen in Table 2, an average decrease of 15% and 18% was noted in abacavir AUC and C_{max} . Although the significance of the decreased exposure to abacavir is not known, it is unlikely that this decrease will be clinically significant.

Effect of abacavir on methadone

The mean plasma methadone concentration-time profiles on Days 14 and 28 are shown in Figure 2 and the pharmacokinetic parameters are summarized in Table 3. The dose

of methadone was the same on Days 14 and 28 for all subjects with the exception of one subject. In Subject 856, the methadone dose was increased from 55 mg to 60 mg on Day 18. There were other minor deviations from the protocol, which probably did not affect the overall outcome of this study.

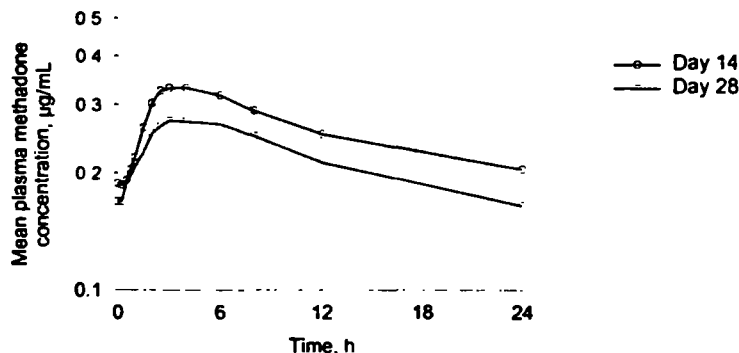


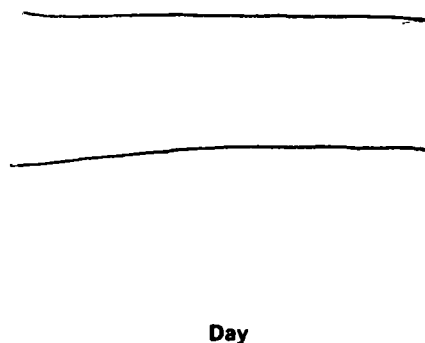
Figure 2

Table 3. Mean (%CV) pharmacokinetic parameters of methadone on Days 14 and 28

PK parameter	Day 14 (n = 11)	Day 28 (n = 11)	Day 28 / Day 14 ratio [90% CI] **
CL/F, L/h	10.87 (49)	13.96 (58)	1.22 [1.06 – 1.42]
Half-life, h	29.5 (33)	26.7 (31)	0.90 [0.80 – 1.02]
CLr, L/h	1.61 (91)	2.01 (113)	1.14 [0.77 – 1.69]
* C _{max} , µg/mL	0.35 (51)	0.29 (45)	0.83 [0.71 – 0.97]
* AUC ₂₄ , µg.h/mL	6.20 (55)	5.19 (49)	0.82 [0.71 – 0.96]

* Not all subjects received the same dose ** Ratios and 90% CI are based on geometric means

The average increase in methadone clearance was 22% when administered with abacavir. In individual subjects, the change in clearance ranged from — decrease to — increase. A stick plot depicting the change in clearance in individual subjects is shown below.



It was noted that methadone clearance was increased by 20% or more in 5 out of 11 subjects when methadone was administered with abacavir. Further, according to the Applicant, post hoc analysis of clearance values without the subject who exhibited the

131% increase resulted in an average increase of 15% in methadone clearance, which was also found to be statistically significant.

CONCLUSIONS: The conclusions of this study are:

- (a) A decrease in the exposure to abacavir was noted when this nucleoside analog was administered with methadone. This decrease in exposure is probably not clinically significant. It was also noted that abacavir was administered at a dose of 600-mg BID while the recommended dose of abacavir is 300-mg BID. The pharmacokinetic interaction between abacavir (at the recommended dose) and methadone is not known.
- (b) Methadone clearance was increased by 20% or more in 5 out of 11 subjects enrolled in this study when methadone was administered with abacavir. Since there is a likelihood of decreased exposure to methadone when patients receive both methadone and abacavir, patients should be monitored for symptoms of withdrawal. The pharmacokinetic interaction between abacavir (at the recommended dose) and methadone is not known.

/S/

Prabhu Rajagopalan, Ph. D.
Senior Clinical Pharmacology and Biopharmaceutics Reviewer
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Concurrence:

7-20-2000

Kellie Reynolds, Ph.D.
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-530 /NDA 20977
/MO/Martin
/RPM/Truffa
HFD-880 /Rajagopalan
/Reynolds

c:\Data\WDA\20977_SE8002\Review.doc

PHARMACOLOGIST'S REVIEW

**NDA 20-977&
NDA 20-978** NDA Efficacy Supplements
Date Submitted: 12/17/99
Date Assigned: 2/2/00
Date Review Completed: 2/18/00
HFD-530

SPONSOR GlaxoWellcome
North Carolina, US

DRUGS Abacavir (Ziagen™)

INFORMATION TO SPONSOR: No

INDICATION Treatment of HIV Infection

COMMENTS

This is an efficacy supplement of abacavir sulfate tablets (NDA 20-977) and oral solution (NDA 20-978) containing 24 and 48 week safety and efficacy data from Trial 3005 and methadone interaction study. The two NDAs received accelerated approvals on 12/17/98 and are presently seeking some changes in clinical information in the label. All preclinical information are cross-referenced to the NDAs and reviewed previously by Dr. Owen McMaster. No additional pharm/tox information was included in the new submission and no changes in pharmacology/toxicology section of the drug label are intended. No regulatory comments on pharm/tox will be provided to the sponsor.

/S/

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:

HFD-530/DepDir/WDempsey 151
HFD-530/PTL/JFarrel 151
Wu/Pharm/2/18/2000 151
Disk: PTL/JFarrelly 151

cc:

HFD-530 Original NDA
HFD-530/Division File
HFD-530/CSO
HFD-530/Pharm/KWu
HFD-345

**DIVISION OF ANTIVIRAL DRUG
PRODUCTS
HFD 530**

MEDICAL OFFICER REVIEW

OF

EFFICACY AND LABELING SUPPLEMENT

sNDA 20-977 and 20-978/SE8-002

**ZIAGEN® (ABACAVIR SULFATE)
TABLETS AND ORAL SOLUTION**

**Medical Officer:
Ekopimo O. Ibia, M.D.**

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1 GENERAL INFORMATION

1.1 APPLICANT IDENTIFICATION

GlaxoWellcome Inc. Five Moore Drive, P.O. Box 13398, Research Triangle Park
North Carolina 27709. Telephone 919 248 2100

1.2 SUBMISSION/REVIEW DATES

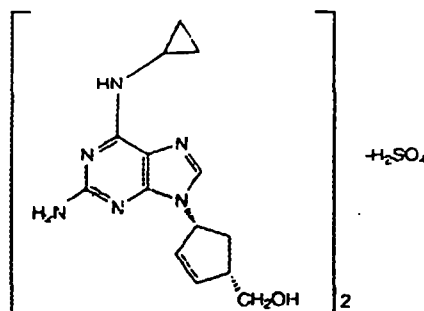
Date of submission: December 16, 1999
Date received: December 17, 1999
Date assigned: January 4, 2000
Date Review Completed: May 31, 2000
Date Written Review Completed: May 31, 2000
Date Revised Review Completed: November 22, 2000

1.3 DRUG IDENTIFICATION

Generic Name: Abacavir sulfate
Trade Name: Ziagen TM
Chemical Name: (1*S,cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1).

Code Name: 1592U89

Chemical Structure:



Molecular Formula: (C₁₄H₁₈N₆O)₂·H₂SO₄
Molecular Weight: 670.76

1.4 PHARMACOLOGIC CATEGORY: Carbocyclic nucleoside analogue inhibitor of
HIV reverse transcriptase

1.5 DOSAGE FORMS: Tablets containing 300mg of abacavir sulfate.

1.6 ROUTE OF ADMINISTRATION: Oral

1.7 PROPOSED INDICATION: Treatment of HIV infection

1.8 RELATED DRUGS: None

1.9 RELATED IND: IND 45,331

2 EXECUTIVE SUMMARY

2.1 RECOMMENDATIONS

The 48 week efficacy and safety results from study CNAAB3005 provided in this submission support evidence of a durable antiviral effect for abacavir in combination with other antiretroviral agents for the treatment of HIV infection. Based on these results, this supplemental NDA should be approved. However, at least two studies demonstrating clinical benefit are required in order to grant traditional approval. While the inclusion in labeling of the durability of antiviral effect of abacavir provided by the 48 week results of study 3005 presents important information to clinicians, traditional approval must await the results of a second study. Potentially fatal hypersensitivity (HSR) reaction to abacavir remains a major concern with this drug. Data from Study 3005 in this submission reports the highest rate of HSR in any clinical trial of abacavir. Furthermore, this review has noted a number of adverse cardiac events in this and other abacavir trials as well as cases of deterioration of depressive illnesses. The exact relationship of these events to abacavir remains unclear. Nonetheless, there is sufficient evidence in this submission for approval to be granted.

2.2 SUMMARY OF CLINICAL FINDINGS

2.2.1 Brief Overview of Submission

In this submission the applicant presents results from two studies:

CNAA1012 "A study to evaluate the pharmacokinetics of abacavir (1592U89) and methadone following co-administration."

CNAAB3005 "A phase III randomized, double-blind, multicenter study to evaluate the safety and efficacy of 3TC/ZDV/1592U89 and 3TC/ZDV/IDV in HIV-1 infected antiretroviral therapy naïve subjects."

Study CNAAB3005 was a 48-week, multicenter, double blind, randomized trial in treatment-naïve HIV-infected subjects. This study compared the safety and efficacy of twice daily abacavir 300 mg with indinavir 800 mg eight hourly. Each was given in combination with twice daily Combivir™. Two final reports for this second study are included in this submission, one report presents the 24 Week study results while the other presents the 48 Week results. The review will focus on the 48 Week data.

2.2.2 Efficacy

The results of this study demonstrated that the proportion of subjects treated with ABC/3TC/ZDV who achieved plasma HIV-1 RNA ≤ 400 copies/mL at Week 48 was equivalent to those treated with IDV/3TC/ZDV. Equivalent increases in CD4+ cell counts at Week 48 were observed for the two treatment groups. These data provide evidence that treatment with abacavir in combination with two other nucleosides lowers viral load and increases CD4 counts through 48 weeks of treatment, and is similar to treatment with a protease inhibitor-containing regimen. However, among subjects with HIV-1 RNA $>100,000$ copies/mL at baseline, ABC/3TC/ZDV was somewhat inferior to IDV/3TC/ZDV. Therefore, it appears that the abacavir-containing combination may be less efficacious in those patients who have a high baseline viral load.

2.2.3 Safety

In study CNAAB3005 hypersensitivity reactions occurred in 7.6% of subjects exposed to abacavir, the highest rate so far recorded in clinical trials of abacavir. In addition, results from study 3005 show that disorders of lipid metabolism occurred to the same extent with the triple nucleoside combination as with the protease inhibitor-containing regimen. Four deaths occurred in subjects on the abacavir arm versus one on the indinavir arm. While the single death on the indinavir arm was possibly due to illicit drug overdose, two of the deaths on the abacavir arm were due to cardiac adverse events and one was a possible hypersensitivity reaction. The cause of the fourth death is unclear but was probably a result of hepatocellular carcinoma. Finally, the extent to which adverse cardiac events and deterioration of depressive illnesses observed in subjects exposed to abacavir can be attributed to abacavir remains unclear and needs further examination.

2.2.4 Study Population

Study 3005 enrolled a relatively healthy adult HIV-infected population under 65 years old. No significant gender or ethnic/racial differences were found in pharmacology, efficacy and safety, although the study was not powered to detect such differences. Regional differences were, however, noted in the response rate and the rate of HSR to abacavir. In both arms, response rates were consistently higher from study centers outside the US. Similarly, higher rates of abacavir HSR were recorded from centers outside the US. No explicit reasons emerged for these differences although these findings may well reflect the peculiarities of multiple subgroup analyses.

3 CLINICAL REVIEW

3.1 INTRODUCTION AND BACKGROUND

3.1.1 Overview of Current Treatment of HIV Infection

Significant progress has been made in the last decade in understanding the biology of human immunodeficiency virus (HIV). With this advancement in knowledge, new drugs have been developed for treatment of this once almost uniformly fatal, now turned chronic, infection. Treatment of the HIV-infected patient with currently available highly active antiretroviral therapy (HAART) results in the slowing of disease progression as measured by surrogate markers (viral load and CD4+ cell counts). Even so, studies are ongoing to establish the optimal therapy for this condition. It is agreed that monotherapy no longer has any role in treatment of these patients.

Combination therapy has proven the most effective approach to treat HIV disease. The current recommended initial antiretroviral regimens include a combination of two nucleoside analogue reverse transcriptase inhibitors (NRTI) and a protease inhibitor (PI); two NRTIs and a nonnucleoside reverse transcriptase inhibitor (NNRTI); or two NRTIs with two PIs. This double PI regimen exploits the pharmacokinetic advantages of low-dose ritonavir (100-200 mg twice daily) in inhibiting cytochrome P450 enzymes. This combination has been shown to improve pharmacokinetic profiles of saquinavir, indinavir, and amprenavir.¹ Such combination may result in enhanced potency, reduced pill burden and improved adherence. Other initial regimens being evaluated include three NRTIs together or a combination of one each of a PI, NRTI, and an NNRTI.¹ In the future, therapies will target other aspects of the HIV biology such as inhibition of viral-host cell fusion. Ultimately, technological advancement will enable vaccine-prevention of this modern day scourge.

Abacavir is a selective inhibitor of HIV replication. The drug is a carbocyclic nucleoside analogue with good oral bioavailability and penetration of the central nervous system.² Abacavir is synergistic (*in vitro*) with zidovudine, nevirapine, and amprenavir and is at least additive to lamivudine, dideoxycytosine, didanosine, and stavudine. Earlier trials have shown efficacy of abacavir to be superior to two nucleoside analogues.

The following is excerpted from the applicant's submission. Abacavir is rapidly absorbed following oral administration with an elimination half-life of 1.54 ± 0.63 hours after a single dose. Food has no significant effect on the systemic exposure of abacavir. Abacavir distributes well into extravascular space and into erythrocytes. Binding of abacavir to human plasma protein is about 50%. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (as the 5'-carboxylic acid (30%)) and glucuronyl transferase (as the 5'-glucuronide (36%)). The resulting metabolites do not possess antiviral activity. Sixteen percent of administered abacavir is eliminated in the feces, 1.2% of intact drug and 15% of unidentified minor metabolites respectively are excreted in urine. Abacavir does not inhibit human cytochrome CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations. It is therefore, unlikely that

clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways. Abacavir shares common metabolic pathway with zidovudine (via glucuronyl transferase) and ethanol (via alcohol dehydrogenase). However, no clinically significant interactions have been documented when abacavir has been taken with each of these agents. With these features, abacavir has a role in the treatment of HIV infection.

Abacavir tablets (NDA 20-977) and oral solution (NDA 20-978) were granted accelerated approval on December 17, 1998 under 21 CFR 314 Subpart H. In the course of the review of above NDAs prior to approval, potentially fatal hypersensitivity reactions to abacavir were identified. Approval of abacavir included phase 4 commitments to carry out a comprehensive study of hypersensitivity reactions within defined timelines.

3.1.2 International Marketing Experience for Abacavir

As contained in this submission and shown on Table A of the Appendix, abacavir has been approved in 29 countries worldwide. No drug product containing abacavir has been withdrawn from marketing in any country.

3.1.3 Applicant's Rationale for this Submission

In the course of the initial review of abacavir prior to accelerated approval, preliminary 16-week results of study CNAAB3005 were considered critical to understanding the overall clinical benefits of abacavir at the time of approval. Because only a very brief description of the results of study CNAAB3005 are currently included in the abacavir label, the applicant considers the 48 week results of study CNAAB3005 important information for prescribers and patients to be included in the package insert.

Medical officer comment: It should be noted that traditional approval of abacavir requires two 48 week studies.

3.2 CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEW DISCIPLINES

No Pharmacology/Toxicology or Chemistry, Manufacturing, and Controls data were submitted with this supplement NDA.

3.2.1 Microbiology Review

Resistance Analysis

The most predominant reverse transcriptase mutation in Study 3005 is M184V. In subjects who failed, the frequencies of M184V mutation were 16/21 (76%) and 9/18 (50%) for abacavir and indinavir arms respectively. The higher rate of mutation of this enzyme in the abacavir treatment arm may reflect the combined effect of both abacavir and Combivir™. No major mutations associated with resistance to indinavir or other protease inhibitors were detected in post-therapy HIV-1 isolates from patients in the indinavir arm. The cases of protease mutations in both arms observed in this study were

due to the known natural polymorphisms of this enzyme based on the amino acid changes detected. These mutations were not likely to be a result of new mutation induced by study medications. These polymorphisms are not known to confer phenotypic resistance to HIV-1 protease inhibitors. Although the data, as submitted, presents no reason to raise new concerns about viral resistance, the package insert will be revised to reflect the findings of this study. For details, please see the review by Lalji Mishra, Ph.D.

3.2.2 Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics review was limited to the methadone interaction study (Protocol CNA 1012). This was an open-label pharmacokinetic (PK) study of interaction between abacavir and methadone. In this study, conducted at two centers in the US and Canada, 17 of 19 enrolled subjects received oral abacavir 300 mg BID plus methadone at escalating doses up to 40 mg or greater daily dose. From Day 15 of treatment, the subjects received 600 mg BID of abacavir but maintained the same constant daily dose of methadone. Eleven subjects completed the entire treatment phase of 28 days. The study showed that abacavir C_{max} was reduced 35% and delayed 0.89 hour with AUC unchanged. There was a 22% increase in methadone $C_{ss/F}$ with 600 mg BID of abacavir but no significant difference in methadone renal clearance. The Biopharmaceutics reviewer noted that coadministration of abacavir and methadone resulted in a decrease of abacavir exposure that is probably not clinically significant and that abacavir was administered at twice the recommended dose of 300mg twice daily. Methadone clearance was increased by 20% or more in 5 of the 11 subjects who completed the study. The reviewer concluded that potential exists for methadone withdrawal in subjects on the two medications and that close monitoring of such patients was necessary. Appropriate label changes are being made in the light of this study result. For details, the reader should refer to the review by Prabhu Rajagopalan, Ph.D.

3.3 REVIEW METHODS

Review of this supplemental NDA was multidisciplinary, involving the clinical, statistical, microbiology, biopharmaceutical, pharmacology/toxicology, and chemistry reviewers with coordination by a project manager. The submission was formally discussed as part of the weekly Team meetings. In addition, several joint formal clinical-statistical and global assessment meetings were held to discuss progress with the review. Furthermore, numerous informal discussions and exchanges took place between the clinical reviewer and reviewers from other disciplines. Where necessary, discussions and requests were channeled directly to the applicant through the project manager. The Division Director and Deputy regularly facilitated the entire review process.

Materials reviewed included relevant clinical sections of the 36 volumes of submitted document (including review of case narratives of subjects with serious adverse events). In conjunction with the statistical reviewer, Andrei Breazna, Ph.D., electronic databases containing the 24 and 48 Weeks data that accompanied the submission and an additional electronic data requested by the review team were all reviewed. Furthermore, written clinical review of original NDA was consulted extensively. In addition, case report forms

(CRFs) from subjects who withdrew or discontinued randomized treatment as a result of adverse event were also reviewed. Also, 38 additional CRFs of subjects with grades 3 and 4 creatine phosphokinase (CPK) elevation were obtained and reviewed. Finally, relevant published literature was reviewed where appropriate.

3.4 DESCRIPTION OF DATA SOURCES

Table 1 summarizes the studies included in this submission as the primary source data. The only relevant literature cited by the applicant in support of this submission refers to a reported case of hypersensitivity reaction to indinavir.³

Table 1: List of Studies in Submission

Study	Location	Design	Enrolled (N)	Treated (N)	Drug Regimen
CNAA1012	2 centers in Canada and the US	Open label, pharmacokinetic drug interaction	19	17	Abacavir 300 mg BID D#1-14 then 600 mg BID D#15-28. Methadone escalating doses to ≥ 40 mg D#2-28
CNAAB3005	North America (34 sites), Europe (37), Australia (4)	Randomized, double-blind, placebo-controlled therapy-naïve subjects	562	527	Abacavir/3TC/ZDV (N=282) Indinavir/3TC/ZDV (N=280)

3.5 REVIEW OF CLINICAL STUDY

3.5.1 Protocol CNAAB3005

A phase 3 randomized, double blind, multicenter study to evaluate the safety and efficacy of 1592U89/3TC/ZDV and IDV/3TC/ZDV in HIV-1 infected antiretroviral therapy naïve subjects 48 week report. The following summarizes this study as contained in the applicant's submission.

3.5.1.1 Study Design

This study was designed to compare the safety and efficacy of ABC/3TC/ZDV and IDV/3TC/ZDV over a 48 week period. Study subjects could switch to open label abacavir at Week 48 and could remain on study to 96 weeks. Thus, only 48 weeks of comparative data are available in this submission. According to the applicant, two optional substudies were planned with this study. These are the _____ and _____ substudies, the result of which are not included in this submission. This study was a randomized, double-blind, parallel group, international, multicenter study to evaluate the antiviral effect, durability of response, and safety of ABC/3TC/ZDV versus IDV/3TC/ZDV in antiretroviral-naïve HIV-1 infected adults with plasma HIV-1 RNA $\geq 10,000$ copies/mL and CD4+ cell counts ≥ 100 cells/mm.³ Subjects were stratified by their screening plasma HIV-1 RNA level ($\geq 10,000$ -100,000 copies/mL or $> 100,000$

copies/mL). Subjects were evaluated at baseline, weeks 2 and 4 and every four weeks thereafter till 48 weeks. The study was conducted between November 1997 and June 1999.

3.5.1.2 Virologic Endpoint

This was defined as viral load measured by real time plasma HIV-1 RNA >400 at Week 16 or at every 8 weeks thereafter. Subjects who met the virologic endpoint were eligible for one of three options: 1) continue randomized therapy; 2) discontinue randomized therapy and receive open-label ABC (300 mg BID) and/or IDV (800 mg q8h) and/or 3TC/ZDV (150/300 mg BID) combination tablet (any licensed antiretroviral therapy could be added or substituted); or 3) discontinue all study medication and withdraw from the study.

3.5.1.3 Investigators and Study Administration

3.5.1.3.1 Good Clinical Practice and Study Monitoring

The applicant acknowledges that this study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki, which applied at the time the study was conducted, and in compliance with Title 21, Parts 50 and 56 of the US Code of Federal Regulations and that the study was conducted in accordance with Good Clinical Practice (GCP). Furthermore, various aspects of the study were reviewed and approved by relevant independent ethical committees or institutional review boards. According to the applicant, no monitoring or evaluation committees were used for this study. US sites were monitored by _____.

_____. Sites in Switzerland and Germany were monitored by _____.
_____. The applicant also reports that clinical trial supply logs were kept for drug dispensed and returned in the pharmacy and reviewed by monitoring personnel. However, the applicant admits that no formal reconciliation was performed for drug dispensed and returned.

Medical Officer Comment: Exactly how sites outside US, Switzerland, and Germany were monitored is not specified in the submission. It is uncertain whether nonuse of monitoring or evaluation committees and lack of formal reconciliation of returned clinical supply logs adversely affected data quality and validity.

3.5.1.3.2 Blinding and Treatment Assignment

The study used matching placebos to blind for ABC tablets and IDV capsules respectively. All subjects were required to take 16 tablets a day, based on three times daily dosing regimen, and adhere to the fluid and diet specifications for IDV. Additionally, subjects were required to take 4 x 200mg IDV/IDV placebo capsules every eight hours rather than the marketed 2 x 400mg capsule every eight hours.

Medical Officer's Comments: The relatively large pill burden and need for hydration required of all subjects may have resulted in decreased compliance and adherence.

during the randomized phase of the study. These issues may also have contributed to the relatively large proportion of subjects who were randomized but never initiated therapy.

3.5.1.4 Inclusion and Exclusion Criteria

Subjects were HIV-1 infected antiretroviral-naïve male or female subjects ≥ 16 years of age (or ≥ 18 years of age at applicable sites). The subjects were required to have plasma HIV-1 RNA $\geq 10,000$ copies/mL and CD4+ $\geq 100/\text{mm}^3$ within 21 days of study drug administration. Adequate provision was made to avoid pregnancy exposure to study medications. Other entry criteria were quite standard for this type of study.

3.5.1.5 Evaluation Criteria

3.5.1.5 Primary Efficacy Measures

Plasma HIV-1 RNA viral load and CD4+ cell counts were used to demonstrate primary efficacy.

3.5.1.5.1.1 Plasma HIV-1 RNA

Plasma HIV-1 RNA levels were measured using the Roche Amplicor HIV-1 Monitor test (Version 1.0, standard limit of detection [LOD] = 400 copies/mL). These measurements followed schedule shown on the flow chart as contained in volume 14 page 205 of the submission. Plasma samples were stored for further analysis using the Roche Amplicor HIV-1 Monitor test (version 1.5, ultrasensitive, LOD = 50 copies/mL).

3.5.1.5.1.2 Immunology (CD4+ and CD8+)

Lymphocyte subset analyses (total lymphocyte and absolute and percentage CD4+ and CD8+ cell counts) were conducted using flow cytometry

3.5.1.5.2 Secondary Efficacy Measures

3.5.1.5.2.1 Time to Plasma HIV-1 RNA Event

Time intervals from first dose to a confirmed plasma HIV-1 RNA level greater than 400, 1000, and 5000 copies/mL were measured.

3.5.1.5.2.2 Disease Progression

HIV-1 disease progression was monitored throughout the study. HIV-1 disease progression was defined as the progression from baseline disease status to the occurrence of the first new event based on the 1993 CDC classification.

3.5.1.5.2.3 Resistance analyses

Resistance data were collected for all subjects with virologic failure and for a random subset of subjects that did not have virologic failure. HIV-1 reverse transcriptase and protease genotypes and phenotypes were obtained using standard procedures

3.5.1.5.3 Safety

Safety measures included analyses of adverse events and change from baseline of clinical laboratory tests (hematology and serum chemistry). All subjects exposed to at least one dose of study medication were included in safety evaluation.

3.5.1.6 Methods of Statistical Analysis

The planned sample size was 550 with 275 subjects in each treatment arm. This sample size was calculated to give 90% power with an alpha of 0.05. Sample size determination assumed success rate of 75% in each treatment arm and ability to detect <12% in the difference of proportions.

Medical Officer's Comment: For detailed comments on the appropriateness of various statistical methodologies, the reader should refer to the statistical review by Andrei Breazna, Ph.D.

3.5.1.6.1 Interim Data Analysis

In response to a regulatory review process in Europe, the applicant had prepared an executive summary, which included all available efficacy data on about 75% of enrolled subjects as of March 15, 1999. The applicant reports that during this European activity, the project team at Glaxo Wellcome remained blinded to each individual patient's treatment but that the statistical team did not maintain blinding.

In addition, a preliminary analysis was conducted on the first 200 enrolled subjects in order to detect early treatment group divergence as required by the protocol. Since the arithmetic difference in the proportion of subjects with plasma HIV-1 RNA >400 copies/mL at Week 16 was not more than the protocol-defined 30 points between the two treatment arms, an independent data safety monitoring board (DSMB) was not found necessary following this preliminary analysis.

3.5.1.6 Populations Analyzed

3.5.1.6.1 Primary Efficacy Analysis

The primary population for the efficacy analyses was the intention-to-treat (ITT) population, which consisted of all randomized subjects with data, regardless of treatment received and study outcome and in which missing data = failure.

The proportion of subjects with plasma HIV-1 RNA $\leq$ 400 copies/mL were summarized by study visit and treatment group. The point estimate and two-sided 95% confidence interval of the difference in proportions was calculated for the assessment of equivalence. The average area under the curve minus baseline (AAUCMB) was calculated to assess the treatment effect on log₁₀ plasma HIV-1 RNA levels and absolute CD4+ cell counts at Weeks 24 and 48.

Medical Officer's Comment: The applicant defined equivalence as the point estimate and two-sided 95% confidence interval of the difference in proportions between the two arms that falls within ± 12 . There appears to be no acceptable theoretical basis for the selection of upper and lower bounds of delta as ± 12 in defining equivalence in this type of study. The Division recommends a delta of ± 12 to be used for the sole purpose of

sample size calculation. The Agency's preferred analysis of CD4 response is one comparison of mean or median CD4 counts at 48 weeks.

The distribution of time to event was estimated using Kaplan-Meier product-limit estimates. The Null hypothesis of no treatment effect was evaluated using log-rank test controlling for screening plasma HIV-1 RNA strata. Risk ratios were estimated using Cox's regression while controlling for randomization strata.

3.5.1.7 Results

A total of 562 subjects were randomized, 282 into the ABC arm and 280 into the IDV arm. Thirty-five subjects never initiated the randomized treatment (20/282, 7% ABC/3TC/ZDV versus 15/280, 5% IDV/3TC/ZDV). Two hundred twenty-two subjects discontinued randomized treatment prior to Week 48 (113/262, 44% ABC/3TC/ZDV versus 109/265, 41% IDV/3TC/ZDV). Of these 222 subjects, 28 (11 ABC/3TC/ZDV, 17 IDV/3TC/ZDV) switched to open label treatment and of those 28, 24 completed on non-randomized treatment (9/262, 3% ABC/3TC/ZDV vs 15/265, 6% IDV/3TC/ZDV).

Medical Officer's Comment: From the review of the SAS dataset submitted with this application, 73 of 75 investigator sites enrolled subjects. Seven (9.6%) of the 73 sites each enrolled 1 patient. Another 7 (9.6%) each enrolled over 15 patients. The remaining 59 (80.8%) sites enrolled between 2 and 15 subjects. As shown in Figure 1, the distribution of enrolled subjects by investigator site was balanced between the two treatment groups. Additionally, exclusion of data from any single site is unlikely to affect the result of the study.

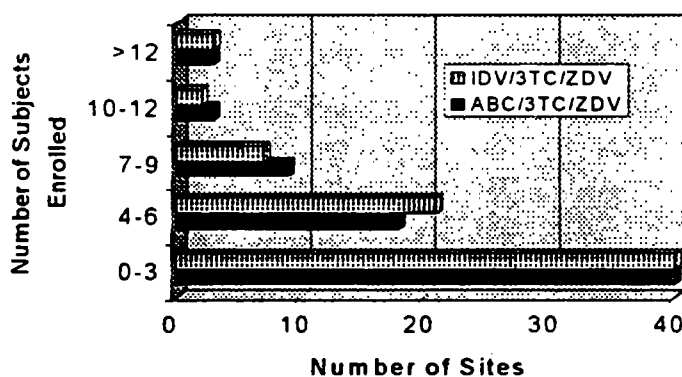


Figure 1. Number of Subjects Enrolled by Treatment Group and Investigator Site

3.5.1.7.1 Description of Study Population

Study subjects were 87% male with a median age of 36 years. Seventy-three percent were white. The majority (72%) were defined as asymptomatic in the CDC classification. At

baseline, median log₁₀ HIV RNA was 4.8 while the median CD4 count was 360 cells/mm.³ Details of baseline characteristics of enrolled subjects are shown on Table 2.

Table 2: Baseline Characteristics

	Treatment groups	
	ABC/3TC/ZDV N=282	IDV/3TC/ZDV N=280
Age at screen (Yrs)		
Median	35.6	36.1
(min, max)	(18.8, 77.3)	(18.8, 66.2)
Sex (n, %)		
Males	246 (87)	241 (86)
Race (n, %)		
Asian	3 (1)	6 (2)
Black	47 (17)	37 (13)
American Hispanic	25 (9)	27 (10)
White	202 (72)	206 (74)
Other	2 (<1)	3 (1)
Missing	3 (1)	1 (<1)
Hepatitis B and C Status		
Hepatitis B Positive Confirmed (n, %)	9 (3)	19 (7)
Hepatitis C Reactive (n, %)	40 (14)	44 (16)
CDC Classification (n, %)		
Asymptomatic	199 (71)	205 (73)
Symptomatic, not AIDS	59 (21)	50 (18)
AIDS	5 (2)	10 (4)
Missing	19 (7)	15 (5)
Median log ₁₀ plasma HIV-1 RNA ^a (N)		
≥ 10,000-100,000 copies/mL	4.61 (N=172)	4.6 (N=171)
> 100,000 copies/mL	5.36 (N=98)	5.23 (N=101)
Total Study Population	4.85 (N=270)	4.82 (N=272)
(min, max)		
Median CD4+ cell count (cells/mm ³) (N)		
≥ 10,000-100,000 copies/mL	407 (N=170)	406 (N=169)
> 100,000 copies/mL	304 (N=98)	289 (N=100)
Total Study Population	359 (N=268)	360 (N=269)
(min, max)		
HIV Risk Factors ^b (n, %)		
Homosexual contact	169 (60)	158 (55)
Injectable drug use	31 (11)	37 (13)
Occupational exposure	0 (0)	2 (<1)
Heterosexual contact	74 (26)	81 (28)
Transfusion	3 (1)	8 (3)
Other	6 (2)	2 (<1)

a As measured by the ROCHE AMPLICOR HIV-1 MONITOR test (Primers v1.0, standard, LOD=400 copies/mL)

b Subjects could have more than one risk factor

Medical Officer's Comments: Baseline characteristics were very similar between the two treatment groups. However, more subjects randomized to IDV arm were hepatitis B and/or C positive compared to those randomized to the ABC arm (23% vs 17%).

Although the exact role of co-infection with these viruses in HIV infected patients is yet to be clearly defined, consensus seems to suggest that such co-infection increases morbidity and mortality.³⁻⁷ It is unclear what impact, if any, this may have on the outcome of this study. Since the study population represented a relatively healthy group of HIV infected patients, it is unlikely that the imbalance in co-infection with these hepatitis viruses affected the outcome of the study.

3.5.1.7.2 Subject Accountability

The Table below gives a summary of subject accountability by treatment group.

Table 3: Subject Accountability

	Treatment Groups	
	ABC/3TC/ZDV	IDV/3TC/ZDV
No. Randomized	282	280
No. Treated	262	265
No. Never Initiated Treatment	20	15
No. (%) Completed 48 Weeks on Study	169 (60) ^a	171 (61) ^a
Completed Randomized Treatment ^b	160	156
Completed on Subsequent Open-label treatment	9	15
No. (%) Discontinued Study Prior to Week 48	113 (40) ^a	109 (39) ^a
Primary Reason for Discontinuing Study Prior to Week 48		
Adverse Event	41	50
Consent Withdrawn	11	6
Lost to Follow-up	21	18
Clinical Progression	2	0
Protocol Violation	3	4
Insufficient Viral Load Response	4	3
Other	11	13
Never Started Treatment	20	15

a Percentages based on number of randomized subjects.

b Includes subjects who discontinued study medication coincident with the Week 48 visit or during the post-treatment follow-up period

Medical Officer's Comment: Subject accountability is balanced between the treatment and comparator groups. Relatively large proportion of subjects in each group (7% and 5% in the ABC and IDV groups respectively) never initiated treatment. The sponsor did not provide reasons why subjects chose to enroll but not initiate study treatments.

3.5.1.7.3 Protocol Deviations

Three (1%) subjects had major protocol violations involving inclusion/exclusion criteria, including 1 subject in the ABC/3TC/ZDV group and 2 subjects in the IDV/3TC/ZDV group. All 3 subjects had an active or ongoing AIDS defining opportunistic infection or disease at study entry.

Medical Officer's Comment: The applicant states that all 3 protocol violations were approved in advance by Glaxo Wellcome medical personnel and are included in all analysis. On Table 4 above, 15 subjects (5 in the ABC/3TC/ZDV group and 10 in the IDV/3TC/ZDV group) had AIDS at baseline and, therefore, violated exclusion criterion

#18. Additionally, 12 subjects in the ABC/3TC/ZDV group and 7 in the IDV/3TC/ZDV group violated various aspects of the entry criteria as shown on Listing 4 of the applicant's submission (volume 15 page 298) and summarized in Table B of the Appendix. These violators were included in the primary efficacy and safety analyses. Their exclusion did not significantly alter the results of the study.

3.5.1.7.4 Concomitant Medications

3.5.1.7.4.1 Concomitant Antiretrovirals

Eight subjects intolerant of ZDV were permitted by the sponsor's medical monitor to change to stavudine (d4T). These subjects were also counted as failures in the sponsor's analysis.

3.5.1.7.4.2 Concomitant Medications Other than Antiretrovirals

Overall, 92% of subjects who initiated randomized treatment used at least one concomitant medication during the first 48 weeks of the study. The most frequent classes of concomitant medications used were drugs acting on the central nervous system, anti-infectives and immunologicals, and gastrointestinal system medications (33% vs 41%). The most commonly used concomitant medications during the first 48 weeks of the study are shown on Table 4.

Table 4: Concomitant Medications Other than Antiretrovirals

	ABC/3TC/ZDV N=262 (n,%)	IDV/3TC/ZDV N=265 (n,%)
Acetaminophen	56 (21)	45 (17)
Multivitamins	47 (18)	40 (15)
Co-trimoxazole	34 (13)	49 (19)
Ibuprofen	47 (18)	31 (12)
Aspirin	25 (10)	26 (10)
Acyclovir	18 (7)	31 (12)
Influenza vaccine	29 (11)	20 (8)
Ascorbic acid	16 (6)	22 (8)
Fluconazole	17 (6)	21 (8)
Ketoconazole	14 (5)	23 (9)

Medical Officer's Comments: Our analysis of these data was in agreement with the applicant's conclusion that, overall, use of concomitant medications was comparable between the two treatment groups.

3.5.1.7.5 Primary Efficacy Results

Table 5 summarizes the outcomes of randomized treatment at Week 48 for the ITT population (missing = failure) as submitted by the applicant.

Table 5: Applicant's Outcome of Randomized Treatment at Week 48 for the ITT Population, Missing = Failure

	ABC/3TC/ZDV N=282 (n (%))	IDV/3TC/ZDV N=280 (n (%))
Plasma HIV-1 RNA ≤ 400 copies/mL	133 (47)	136 (49)
Plasma HIV-1 RNA > 400 copies/mL ^a	36 (13)	23 (8)
Discontinued due to adverse event	43 (15)	55 (20)
Discontinued due to other reasons ^b	48 (17)	48 (17)
Randomized but did not start treatment	20 (7)	15 (5)
Data not available at Week 48	2 (<1)	3 (1)

a. Includes discontinuations due to virologic failure at or before Week 48.

b. Consent withdrawal, lost to follow-up, protocol violation, changed ART, and other.

Medical Officer's Comment: The original SAS dataset submitted by the applicant gave a rather narrow definition of reason for failure (changed ART, confirmed failure, met protocol defined switch criterion, never below 400 copies/mL, no RNA sample). To facilitate review, we obtained from the applicant another SAS dataset to include as reason for failure the following: adverse event, CDC class C event, consent withdrawn, lost to follow up, protocol violation, changed ART, confirmed failure, met protocol defined switch criterion, never below 400 copies/mL, no RNA sample, and other. Analysis of this second dataset revealed inconsistencies with Table 7 above. The sponsor explained these apparent inconsistencies to result from different methods used to analyze the two datasets, proportion of responders at 48 weeks and Kaplan-Meier analysis respectively.

Table 6 shows the proportion of subjects with plasma HIV-1 RNA ≤ 400 copies/mL by randomization stratum and treatment group in the ITT population (missing = failure) as analyzed by the applicant. In this analysis, the applicant alludes to "predefined equivalence limits of ± 12 " and claims that equivalence is demonstrated as the confidence interval of the difference between the treatment and comparator arms are within those limits. As noted elsewhere in this review, the Agency has utilized this limit for the purpose of calculating sample size.

Table 6: Proportions of Subjects with Plasma HIV-1 RNA ≤ 400 copies/mL at Week 48 (ITT, Missing = Failure) Per Applicant's Submission

Randomization Stratum	ABC/3TC/ZDV	IDV/3TC/ZDV
	n/N (%)	
Total Population	133/282 (47)	136/280 (49)
$\geq 10,000$ -100,000 copies/mL	86/180 (48)	79/176 (45)
$> 100,000$ copies/mL	47/102 (46)	57/103 (55)
95% CI of difference in Proportions	(-10, 7)	(-10, 7)

In subjects with baseline plasma HIV-1 RNA $> 100,000$ copies/mL, the proportion of subjects with plasma HIV-1 RNA ≤ 400 copies/mL at Week 48 was 46% for

ABC/3TC/ZDV and 55% for IDV/3TC/ZDV [95% CI (-23%, 4%)]. However, this comparison was not statistically significant.

Medical Officer's Comment: Although there was no statistically significant difference between the two treatment groups in the proportion of subjects with plasma HIV-1 RNA ≥ 400 copies/mL at Week 48, the ABC treatment arm appears to be inferior to IDV treatment arm in subjects who entered the study with a high baseline viral load.

Results of review team reanalysis of the data submitted by the applicant are shown on Tables 7 and 8. For details the reader should refer to the statistical review by Andrei Breazna, Ph.D.

Table 7: Failure rates by week 48 in Different Subpopulations.
DAVDP Analysis

Cohort	Failure rate ABC n/N (%)	Failure rate IDV n/N (%)	Difference in Rate (%) (95% CI)
All*	133/262 (50.8)	133/265 (50.3)	0.5 (-8.3,9.5)
USA**	63/121 (52.1)	69/120 (57.5)	-5.4 (-18.8,7.9)
Non-US**	69/14 (49.3)	63/142 (44.4)	4.9 (-7.4,17.3)
>10,000-100,000 copies/mL***	83/166 (50.0)	85/165 (51.5)	-1.5 (-12.9,9.9)
>100,000 copies/mL***	50/96 (52.1)	47/99 (47.5)	4.6 (-10.4,19.7)
Missing	1/2 (50.0)	2/3 (66.7)	-16.7 (NA)

*All randomized and received at least one dose of treatment

**US vs. Non-US sites

***HIV RNA at baseline

Medical Officer's Comment: The IDV arm tends to perform poorer than the ABC arm at lower baseline viral loads while at the same time outperforming ABC at higher baseline viral loads. Although these differences are not statistically significant, this paradox is difficult to interpret and may contribute to the apparent poorer performance of abacavir in subjects with high baseline viral load. Also, as shown on Table 7, regional differences (US vs. non-US sites) may indicate another possible lack of consistency in this trial. The IDV arm appears to have performed significantly better in the non-US sites (Fisher's exact test p-value=0.036). Reasons for these results are not obvious. To further examine for data consistency, outcomes in subjects enrolled in North American (US and Canada) sites were compared with those enrolled in Europe and Australia. Table 8 below summarizes failure rates at 48 Weeks for sites within and outside North America.

Table 8: Failure Rates by region

	Treatment Arm	
	ABC n/N (%)	IDV n/N (%)
North America	79/154 (51.3)	82/156 (52.6)
Australia & Europe	53/107 (49.5)	50/106 (47.2)

Although this breakdown is of limited utility as protocol design was only powered for differences between the two treatment groups from all the sites combined, there is an apparent poorer performance of trial drug and comparator among the North American sites compared with sites in Europe and Australia. The significance of this finding is unclear and may well reflect the result of multiple subgroup analyses. However, if the finding is real, it will need verification in other studies. In summary, although discrepancies are noted on sub-analysis of data, overall response rates are comparable between the two arms.

Table 9 shows the viral load results of utilizing the <50 RNA assay (ultrasensitive) as contained in the submission.

Table 9: Proportions of Subjects with Plasma HIV-1 RNA $\leq$ 50 copies/mL at Week 48 (ITT, Missing = Failure)

Randomization Stratum	ABC/3TC/ZDV	IDV/3TC/ZDV
	n/N (%)	
Total Population	104/282 (37)	121/280 (43)
$\geq 10,000$ -100,000 copies/mL	74/180 (41)	76/176 (43)
>100,000 copies/mL	30/102 (29)	45/103 (44)
95% CI of difference in Proportions	(-15, 2)	(-14, 2)

In subjects with baseline plasma HIV-1 RNA >100,000 copies/mL, the proportion of subjects with plasma HIV-1 RNA $\leq$ 50 copies/mL at Week 48 was 29% for ABC/3TC/ZDV and 44% for IDV/3TC/ZDV [95% CI (-27%, -1%)]. This difference was statistically significant

Medical Officer's Comment: As noted earlier, fewer subjects who had viral load $\geq 100,000$ copies/mL at baseline treated with ABC reached the protocol defined endpoint of < 400 copies/mL at 48 weeks compared with those on IDV arm. This difference was more marked when the results of the ultrasensitive HIV RNA viral load assay (LOD = 50 copies/mL) were evaluated. However, for the ultrasensitive assay, applicant performed analyses at three time points with small sample sizes resulting in wide confidence intervals. In addition, review statisticians were unable to reproduce the results of the ultrasensitive analyses. As a result of these, the significance of the findings from the ultrasensitive analyses is not clear.

Table 10: Median CD4+ Cell Count AAUCMB through Week 48 for ITT Population (LOCF)

	ABC/3TC/ZDV	IDV/3TC/ZDV
	Cells/mm ³ (N)	
Total Population	107 (225)	93 (234)
$\geq 10,000$ -100,000 copies/mL	96 (141)	85 (143)
>100,000 copies/mL	117 (84)	115 (91)
	95% CI: (-24, 19)	

Medical Officer's Comment: Analysis by the review statisticians of CD4+ cell count median change from baseline at Week 48 were comparable between the two arms (152 ± 10.52 cells/mm³ for the abacavir group (N=204) and 149 ± 10.23 cells/mm³ for the indinavir group (N=220)).

3.5.1.7.6 Secondary Efficacy Measures

Secondary efficacy measures examined time-to-plasma HIV-1 RNA event at the 400 copies/mL threshold, disease progression, and resistance data.

3.5.1.7.6.1 Time to Plasma HIV-1 RNA Event

Table 11 shows results of the time-to-event analysis.

**Table 11: Time to Plasma HIV-1 RNA Event at the 400 copies/mL Threshold
Proportion of Subjects with HIV-1 RNA >400 copies/mL**

Week of Estimate	ABC/3TC/ZDV (N=262)	IDV/3TC/ZDV (N=265)
0-8	17	16
8-16	21	21
16-24	27	27
24-32	33	30
32-40	34	32
40-48	37	35

Median Plasma HIV-1 RNA Change from Baseline at Week 48 [ITT (LOCF)] for ABC/3TC/ZDV group and IDV/3TC/ZDV group was $-2.04 \log_{10}$ and $-2.02 \log_{10}$ respectively. Median Change from Baseline CD4+ Cell Counts at Week 48 [ITT (LOCF)] for ABC/3TC/ZDV group and IDV/3TC/ZDV group was 149 and 142 respectively

3.5.1.7.6.2 Disease Progression

Table 12 shows Agency's summary of disease progression

Table 12: Summary of Disease Progression by Treatment Group Through Week 48

Disease Progression ^a	ABC/3TC/ZDV	IDV/3TC/ZDV
A – B	10	6
B – C	3	0
A – C	2	1
C – New C	1	1
Total	16	8

^a Based on CDC Classification

Table 13 lists all subjects who progressed to class C disease.

Table 13: Progression to Class C Event

Treatment Group/Subject ID No.	Event	Time to Event (Week)
ABC (N=6)		
5514	KS, cutaneous (not confirmed)	-5
5651	Mycobacterium avium complex or Kansaii (not confirmed)	31
5994	Cytomegalovirus disease (not confirmed)	4
7243	KS, cutaneous	36
7917	KS, cutaneous (confirmed); KS, visceral (not confirmed)	10
7935	Cryptococcosis (confirmed)	1
IDV (N=2)		
6419	Primary Lymphoma of Brain (not confirmed)	1
7282	KS, cutaneous (confirmed, but at study Day -2)	Study Day -2

Table 14: Deaths

Treatment Group/Subject ID No.	Event	Time to Event (Week)
ABC (N=4)		
5443	Death, cardiac arrhythmia	30
6493	Death, myocardial infarction	35
8103	Death, Possible hypersensitivity Reaction	3
7166	Death, Possible Hepatocellular carcinoma	73
IDV (N=1)		
6147	Death, Possible overdose of illicit drugs	7

Medical Officer's Comment: An additional death was noted on reviewing case narratives of serious adverse events. This was a 41 year old male with a history of hepatitis randomized to the abacavir arm. He was diagnosed with hepatocellular carcinoma approximately 18 months after starting study medication. The patient had withdrawn from the study 8 days following diagnosis and died at home three days later. This death is included in Table 14 above.

One of the class C disease progressors listed in the submission (Volume 14 Page 70) was identified as subject number 6611 with a diagnosis of unconfirmed Cytomegalovirus disease. We could find no documents for subject with this ID number. Subject number 7243 (diagnosis: cutaneous Kaposi sarcoma) was listed in the case narratives and case report forms but was not included in the list of subjects who died or progressed to Class C (Volume 14 page 70). In response to the Agency's request for clarification, the sponsor admitted error in reporting, noting that the number 6611 is the site investigator number while subject number 7243 had confirmed cutaneous Kaposi sarcoma event. This subject has been included in Table 13.

There were twice as many subjects with disease progression in the ABC group as in the IDV group. Disease progression in majority of the subjects occurred from CDC Class A to B. Of the eight subjects that progressed to Class C or developed new Class C condition, six occurred early in the course of the study. These are, therefore, less likely to indicate treatment failure but rather reflect the trend of the disease prior to initiation of randomized treatment. The remaining two subjects (both in the ABC group) progressed to Class C disease later in the course of the trial. These would more likely be regarded as therapy failures. The imbalance in progression, with more subjects on the ABC arm demonstrating disease progression, may reflect the decreased efficacy of the triple nucleoside regimen in subjects who entered with high viral load.

3.5.1.7.7 Review of Safety

3.5.1.7.7.1 Clinical Adverse Events

Overall, the occurrence of any adverse event was comparable between the two treatment groups (94% for ABC/3TC/ZDV group vs. 96% for the IDV/3TC/ZDV group). Selected clinical and laboratory adverse events are summarized in Tables 15 and 16

Table 15: Selected Clinical Adverse Events^a

Adverse Event	Number of Subjects by Treatment Group	
	ABC/3TC/ZDV N=262	IDV/3TC/ZDV N=264
	n (%)	n (%)
Nausea	157 (60)	160 (61)
Abdominal distension	27 (10)	16 (6)
Gastrointestinal hemorrhage	11 (4)	2 (<1)
Malaise and Fatigue	115 (44)	109 (41)
Temperature regulation disturbance	53 (20)	35 (13)
Chest symptoms	17 (6)	9 (3)
Headache	74 (28)	67 (25)
Breathing disorders	18 (7)	7 (3)
Psychiatric disorders	60 (23)	51 (19)
Disorders of sweat & sebum	24 (9)	66 (25)
Urologic disorders	25 (10)	61 (23)
Cardiovascular disorders	27 (10)	17 (6)

^a Culled from Table 54 of applicant's submission

Table 16: Selected Laboratory Abnormalities^a

Adverse Event	Number of Subjects by Treatment Group	
	ABC/3TC/ZDV N=262	IDV/3TC/ZDV N=264
	n (%)	n (%)
ALT	66 (25)	58 (22)
Amylase	33 (13)	37 (14)
Cholesterol	6 (2)	4 (2)
CPK	104 (40)	90 (34)
Hyperglycemia	110 (42)	129 (49)
Triglycerides	81 (31)	99 (38)
Anemia	10 (4)	12 (5)
Neutropenia	91 (35)	86 (33)

^a Culled from Tables 60 and 61 of applicant's submission

Medical Officer's Comment: *Temperature regulatory disturbances occurred significantly more often among subjects on the ABC treatment arm compared with those on IDV arm. Some of these may be related to ABC hypersensitivity reactions. The approved package insert for abacavir already captures higher rates of fever.*

3.5.1.7.2 Disorders of Lipid Metabolism

A review of the submitted SAS 48 Week dataset reveals a total of 19 subjects with disorders of lipid metabolism (10, ABC/3TC/ZDV and 9, IDV/3TC/ZDV) as presented in Table 17. Detailed listing of subjects with disorders of lipid metabolism is shown on Table C of the Appendix.

Table 17: Disorders of Lipid Metabolism

	ABC/3TC/ZDV	IDV/3TC/ZDV
Lipodystrophy	3	4
Elevated Tryglycerides*	8	3
Elevated Cholesterol	1	1
Hyperlidemia	0	1

* Two of the subjects with lipodystrophy in the ABC/3TC/ZDV group also had elevated triglyceride level

Only one of these disorders of lipid metabolism required interruption or modification of assigned treatment (one subject from IDV/3TC/ZDV group permanently discontinued treatment as a result of lipodystrophy). Although most of these lipid abnormalities were grades 1 or 2 in severity, four subjects on each arm had grade 3 or 4 abnormalities. All four of the higher-grade abnormalities on the ABC arm began between Weeks 7 and 16 of the study. Three on IDV arm started prior to Week 7 while onset of the fourth case was about Week 36.

A comparison with a summary of treatment emergent clinical chemistry abnormalities (during the randomized phase of the study) contained on Table 60 of the applicant's submission shows some discrepancies. Eighty-one cases of triglyceride abnormalities are reported for the ABC arm out of which 5 are grades 3 or 4. For the IDV arm, a total of 99 counts are reported with 3 cases of grades 3 or 4 severity. These discrepancies may be due to multiple occurrences in any single subject or the inclusion of those with below normal levels. It is noteworthy that the triple nucleoside combination should have comparable lipid abnormality profile as a protease inhibitor combined with two nucleoside analogues.

3.5.1.7.3 Serious Adverse Events

Overall, serious adverse events occurred in 55 (21%) and 58 (22%) subjects on the ABC and IDV treatment arms respectively. Selected serious adverse events are shown on Table 18.

Table 18: Selected Serious Adverse Events

	ABC/3TC/ZDV N=262	IDV/3TC/ZDV N=264
	n (%)	n (%)
Abnormal liver function tests	11 (4)	7 (3)
Temperature Regulation Disturbance	6 (2)	1 (<1)
Psychiatry Disorders	6 (2)	1 (<1)
Cardiovascular Disorders	3 (1)	0 (0)
Urologic Disorders	1 (<1)	11 (4)

In evaluating overall safety in this study, four areas are of particular concern. These include:

- Hypersensitivity reaction to abacavir.
- Cardiac adverse events associated with abacavir
- Worsening depressive illnesses in abacavir treated patients

3.5.1.7.3.1 Hypersensitivity Reaction to Abacavir

Complete clinical characterization of abacavir hypersensitivity reactions is still evolving. In clinical trials so far submitted to the Agency, the incidence rates of these reactions have ranged from 0 to 6.7% with a combined average rate of about 5%. There are currently no means of predicting this potentially fatal reaction and there are no tests to confirm diagnosis. There has been no gender, racial or age predilection. The reaction has occurred with similar frequency in all populations of HIV-infected subjects.

A recent review of published and unpublished literature on this drug attempts to define this syndrome and recommends protocol for management.⁸ Although of uncertain validity, the protocol provides a formalized management procedure aimed at minimizing progression of abacavir hypersensitivity reaction.⁸ Hypersensitivity reactions to abacavir usually involve multiple body systems. Time to onset has ranged from 3-56 days with a mean of 11 days.⁸ More rarely, cases have occurred after one or two doses or after months on therapy. Presenting features and severity are also variable. Fever and rash are the most common manifestations. The rash in this reaction may be pleomorphic. Enanthems such as conjunctivitis and oral ulceration may occur. Gastrointestinal symptoms are also prominent and include nausea, abdominal pain, diarrhea and vomiting. Other manifestations include respiratory symptoms, myalgia and arthralgia, malaise, lymphadenopathy, paresthesia and fatigue.⁸

When unrecognized, continued dosing can result in rapid clinical deterioration with acute anaphylaxis, severe hypotension, respiratory failure, liver failure, renal failure and death.⁹ Laboratory derangements that have been reported with abacavir hypersensitivity reactions include leukopenia, elevated liver enzymes, serum creatinine, and creatine phosphokinase.⁸ When recognized early, discontinuation of abacavir usually results in complete recovery within 1 week.⁸

In this submission, the applicant has identified 23 cases of possible abacavir hypersensitivity reactions. The applicant regards only 19 of these as probable or definite hypersensitivity reaction giving an incidence rate of 7.3%. Case identification required that the subject had discontinued medication due to the adverse events, there was evidence of multiple organ-system involvement, and that there was no clearly documented alternative diagnosis to explain the symptoms.

*Medical Officer's Comment: The applicant excluded four of the 23 cases from analysis of hypersensitivity reactions. In one of these cases (#7935), *Cryptococcus neoformans* was isolated from blood and skin lesion during an episode of fever and rash. Another case (#6293) had only rash with no multi-system involvement. A third subject (#7664) had nausea, vomiting, and diarrhea with skin lesion listed as "infected sebaceous cyst." The fourth subject (#5839) developed vomiting, headache, runny nose, rash on arms and neck, diarrhea, and fatigue for which he discontinued study medication. In addition, this patient had lymphadenopathy at about the same time, a condition not present at baseline. Six days later, laboratory tests revealed grade 4 elevation of AST and grade 4 elevations of serum amylase with reportedly normal pancreatic amylase. The applicant did not consider this subject to have developed hypersensitivity reaction "since this case was identified only by utilizing very broad criteria and not by either investigator or algorithm."*

While we agree with the applicant that the first 3 cases are clearly not hypersensitivity reactions, it is difficult to disregard the 4th case. Although this subject was documented to be a heavy user of alcohol and some of the findings may be alcohol-related, it is unlikely that alcohol alone can explain the clustering of symptoms which apparently resolved with discontinuation of study medication. We, therefore, reject the applicant's conclusions and consider this a case of abacavir hypersensitivity reaction.

Using the same methodology to describe hypersensitivity events in subjects who received indinavir is misleading, as this characteristic event has not been described for indinavir. Although allergic-type reactions have been reported with indinavir,¹⁰⁻¹² they are rare and very different from the hypersensitivity reaction associated with abacavir. In addition, patients with indinavir rashes can often continue indinavir with no increased risk of clinical deterioration.¹³ Furthermore, it is possible that milder cases of HSR are omitted using the current case definitions.

Finally, as noted by the applicant, there were regional differences in the rates of hypersensitivity reactions in this study. Eight (4.8%) cases of HSR occurred among 166 subjects enrolled and randomized to ABC in the US and Canada while 11 (9.5%) cases were reported among the 116 subjects enrolled and randomized in Europe and Australia. In summary, the applicant identified 19 cases of ABC hypersensitivity in this study giving a rate of 7.3%. We have identified an additional case, bringing the overall rate of HSR in this study to 7.6%. This later case was enrolled in the US, thus bringing the rate for the US and Canada to 5.4%. Table 19 summarizes incidence rates of abacavir hypersensitivity reactions in controlled trials of abacavir.

**Table 19: Summary of Abacavir Hypersensitivity Reactions (HSR)
in Controlled Trials**

Study Number	Number receiving Abacavir	HSR Cases identified by applicant	HSR cases identified by FDA	Rates % (FDA analysis)
2001	79	3	3	3.8
2002	60	3	4	6.7
2003	32	0	0	0.0
2004	78	4	4	5.1
3001	48	2	3	6.3
3002	91	3	5	5.5
3003	85	4	5	5.9
3006	100	2	3	3.0
3005	262	19	20	7.6
Total	835	40	47	5.6

3.5.1.7.7.3.2 Cardiac adverse events in recipients of abacavir

The applicant has documented two cases of fatal cardiac events in the current submission (Subject #5443-fatal cardiac arrhythmia in a 37 year old male, subject #6493-fatal myocardial infarction in a 35 year old male). In addition, we noted a subject (#7634) with atrial fibrillation on two occasions while on study medication. There was no cardiovascular medical condition at baseline.

In the Annual Report for abacavir covering the period from May 2, 1998 to May 1, 1999, seventeen additional cases of myocardial infarctions were noted. From July 20 forward, at least six more cases of myocardial infarction have been reported in patients receiving abacavir. These excluded other cardiac-related events such as angina, congestive heart failure, arrhythmia, cardiomyopathy and cardiac arrest. These events are summarized in Tables D and E in the Appendix. Although attributability of these events to abacavir is difficult, given the co-morbidities in this patient population and the concomitant medications, it should be noted that many of these cardiac events occur in those under 45 years of age.

3.5.1.7.7.3.3 Worsening of Depression in Abacavir Treated Subjects

In reviewing the case narratives of serious adverse events and CRFs of subjects who discontinued or withdrew due to an adverse event, we identified five subjects (Subject #s 7823, 7668, 8152, 7468, and 5194) whose depressive illnesses significantly worsened while in the study. All five subjects were receiving abacavir treatment. The event occurred within 2-5 weeks after starting study medication in four of the subjects and after 42 weeks in the 5th subject.

Details of these are shown in Table 20 below. The incidence of depressive disorders in this study was 10% in the abacavir arm and 9% in the indinavir arm. Similar worsening of depression attributed to treatment with abacavir has not been noted in previous clinical trials.

Table 20: Worsening Depressive Illnesses in ABC Treatment Arm

Subject ID#	Study Arm	Duration on Study Prior to Event	Baseline Psychiatric History	Concomitant Anti-depressant	Psychiatric Event
7823	ABC	5 weeks	Past history of drug abuse and attempted suicide. Controlled at study entry	Not stated	Attempted Suicide. <i>Baseline data altered to include previous depression and attempted suicide.</i>
7668	ABC	3 weeks	Treated for depression for 12 months prior to entry	Fluoxetine, thioridazine	Suicidal tendencies
8152	ABC	2 weeks	A "little depressed" prior to study entry	Not stated	Worsened depression
7468	ABC	42 weeks	History of ongoing depression	Not stated	Depressed with thoughts of self-harm and suicidal tendencies. Overdose with temazepam
5194	ABC	5 weeks	History of depression	Not stated	Worsened depression

3.5.1.7.4 Pregnancy Exposure to Study Medications

Four pregnancies were reported among three subjects during the first 48 weeks of the study. The first was exposed to IDV and was terminated via elective abortion. The second was also exposed to IDV and resulted in a healthy, uninfected term male infant. The third was initially exposed to ABC and resulted in spontaneous abortion at 10.5 weeks of pregnancy. The subject was restarted on Combivir™ and IDV and had a second pregnancy 2 months later. The outcome of the latter pregnancy was not known at time of the report.

3.5.1.8 Gender and Race Differences

Study 3005 enrolled a relatively healthy adult HIV-infected population under 65 years old. No significant gender or ethnic/racial differences were found in efficacy and safety, although the study was not powered to detect such differences.

4 LABELING COMMENTS

The Adverse Event, Drug Resistance, Drug Interactions, and Description of Clinical Trial sections of the label were revised to incorporate new findings from Protocol 3005. Labeling of cardiac events will require analysis by Office of Post-Marketing Drug Risk Assessment (OPDRA). We have requested a consult on post-marketing events from OPDRA as well as an analysis of cardiac events from the sponsor.

5 CONCLUSIONS

The results from study 3005 support the 48 week efficacy of abacavir in combination with other antiretroviral agents for the treatment of HIV infection. In this study, ABC 300 mg twice daily was demonstrated to have similar efficacy compared to IDV 800 mg twice daily both given in combination with twice daily Combivir.™

The primary efficacy analyses used surrogate markers based on proportion of subjects with plasma HIV-1 RNA viral load ≤ 400 copies/mL and CD4+ cell counts at Week 48. The results of the randomized study show that in the population of HIV-1 infected subjects studied:

- In subjects with baseline plasma HIV-1 RNA viral load $< 100,000$ copies/mL, ABC/3TC/AZT performed as well as IDV/3TC/AZT and suppression of HIV-1 was equally durable between the two groups.
- In subjects with plasma HIV-1 RNA viral load $> 100,000$ copies/mL, ABC/3TC/AZT was somewhat inferior to IDV/3TC/AZT.

Potentially fatal hypersensitivity reactions remain a significant risk from abacavir therapy. The rate of HSR of 7.6% in this submission constitutes the highest rate so far documented in any abacavir-related clinical trial. The applicant has committed to an extensive plan to study these reactions as contained in the initial approval letter (See Appendix F). In addition, adverse cardiac events have been reported in this trial, as were cases of deterioration of depressive illnesses. The relationship of these events to abacavir is unclear at this time, and a further evaluation of these events is planned. Finally, we note with interest comparable disorders of lipid metabolism between abacavir arm (a triple nucleoside regimen) and indinavir arm (protease inhibitor regimen).

6 RECOMMENDATIONS

Based on the efficacy and safety information submitted in sNDA 20-977, abacavir 300 mg twice given twice daily in combination with other antiretroviral agents. This supplement, which will provide for inclusion of the 48 week results from study 3005, should be approved. It should be noted that a second 48 week study to support traditional approval of abacavir will be required.

/s/

Ekopimo Ibia, M.D.
Medical Officer, DAVDP

Concurrences:

HFD-530/Director/Hjolson

HFD-530/Team Leader/TCvetkovich 15 11/29/00

Cc:

HFD-530/NDA 20-977

HFD-530/NDA 20-978

HFD-530/Division File

HFD-530/Biopharm/McMaster, Rajagopalan

HFD-530/Chem/Khambampati

HFD-530/Micro/Mishra

HFD-530/MO/Ibia, Martin, Cvetkovich *Eo1*

HFD-530/Stat/Breazna, Aras

HFD-530/Project Manager/Truffa

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Appendix**Table A: International Marketing Experience for Abacavir**

Country	Approved Date
USA	12/17/98
Israel	12/27/98
New Zealand	02/25/99
Argentina	02/26/99
Mexico	03/02/99
Brazil	03/15/99
Uruguay	04/29/99
Australia	06/01/99
Canada	06/04/99
Switzerland	06/28/99
EC Austria	07/08/99
EC Belgium	07/08/99
EC Denmark	07/08/99
EC Finland	07/08/99
EC France	07/08/99
EC Germany	07/08/99
EC Greece	07/08/99
EC The Netherlands	07/08/99
EC Ireland	07/08/99
EC Italy	07/08/99
EC Luxembourg	07/08/99
EC Portugal	07/08/99
EC Spain	07/08/99
EC Sweden	07/08/99
EC UK	07/08/99
Botswana	08/25/99
Chile	08/31/99
Singapore	09/01/99
Ghana	09/15/99

EC = European Community

Table B: Protocol Violation

Treatment Group	Subject #	Criteria Violated
ABC/3TC/ZDV	6414	Lab results within 14 days of treatment: Serum bilirubin >1.5 ULN
	6416	Subject not antiretroviral naïve
	6071	Lab results within 14 days of treatment: ANC <1000
	5651	Subject not antiretroviral naïve
	5847	Subject did not have a single screening viral load assessment $\geq 10,000$ copies/mL within 14 days prior to study drug administration
	7664	Lab results within 14 days of treatment: ANC <1000
	7202	Subject did not have a single screening CD 4 lymphocyte cell count ≥ 100 cells/mm ³ within 14 days prior to study drug administration
	7224	Subject did not have a single screening CD 4 lymphocyte cell count ≥ 100 cells/mm ³ within 14 days prior to study drug administration
	6065	Lab results within 14 days of treatment: Serum pancreatic amylase >1.5 ULN
	7203	Subject did not have a single screening CD 4 lymphocyte cell count ≥ 100 cells/mm ³ within 14 days prior to study drug administration
	7392	Lab results within 14 days of treatment: Serum pancreatic amylase >1.5 ULN
	8228	Lab results within 14 days of treatment: Platelet count < 75,000 cells/mm ³
IDV/3TC/ZDV	7205	Lab results within 14 days of treatment: Platelet count < 75,000 cells/mm ³
	7207	Subject did not have a single screening CD 4 lymphocyte cell count ≥ 100 cells/mm ³ within 14 days prior to study drug administration
	7233	Lab results within 14 days of treatment: Platelet count < 75,000 cells/mm ³
	5289	Subject was not antiretroviral naïve
	5505	Lab results within 14 days of treatment: Serum pancreatic amylase >1.5 ULN
	7216	Lab results within 14 days of treatment: AST or ALT >5 times ULN
	8171	Subject did not have a single screening viral load assessment $\geq 10,000$ copies/mL within 14 days prior to study drug administration Lab results within 14 days of treatment: ANC <1000

Table C: Detailed List of Subjects with Disorders of Lipid Metabolism

Subject /Treatment Arm	Lipid Abnormality	Grade	Approximate Weeks on Study
ABC/3TC/ZDV			
5642	Elevated Triglycerides	4	4
5642	Elevated Triglycerides	3	7
5643	Increased Hypercholesterolemia	n/a	7
5990	Elevated Triglycerides	3	16
7146	Lipodystrophy	n/a	25
7178	Elevated Triglycerides	3	11
7410	Elevated Triglycerides	2	2
7490	Elevated Triglycerides	1	2
7497	Elevated Triglycerides	2	4
7497	Lipodystrophy	n/a	20
7497	Elevated Triglycerides	1	36
7538	Lipodystrophy	n/a	16
7538	Elevated Triglycerides	1	28
7538	Lipodystrophy	n/a	31
IDV/3TC/ZDV			
5297	Hypercholesterolemia	3	Date of first dose
5347	Elevated Triglycerides	4	36
5940	Hyperlipidemia	2	48
5996	Elevated Triglycerides	4	6
6539	Lipodystrophy	n/a	39
7140	Lipodystrophy	n/a	38
7167	Lipodystrophy	n/a	45
7492	Elevated Triglycerides	3	2
7492	Elevated Triglycerides	2	18
7496	Lipodystrophy	n/a	37

n/a Not available. Data taken from 48 Week SAS dataset submitted by applicant

Table D: Cardiac events in ABC Recipients as Contained in Individual or Quarterly Reports up to March 31, 2000*

Case #	Age/Sex	Adverse Event	Onset Post-ABC	Concomitant Medications	Notes
B363946	41M	MI/arteritis	3M	NFV/NVP	History of hypercholesterolemia, hypertriglyceridemia, smoking
A96691	42F	MI	1.5M	EFV/3TC/D4T or ZDV	Complex medical history. Prior to this regimen, was on 2 PIs + NRTI
A74502	40M	MI	19W	NFV/NVP	Smoker, history of deep venous thrombosis, mild obesity
B367882	35M	Angina/ischemia/CA thrombosis		EFV/D4T	History of arteriopathy (leg(s)), hyperlipidemia, diabetes, smoking, increased weight, MI 1.5y prior to ABC
B367878	51M	Cardiac failure, chest pain, dyspnea, fatigue, mitral incompetence	3M	NVP/NFV/D4T/3TC	History of mitral insufficiency, smoking
A71327	69F	Congestive heart failure			History of long-standing congestive heart failure
B366727	33F	Unstable angina, possible MI	3.5W	APV/3TC/ZDV/EFV	Chest pain, initially considered possible MI (France)
B366646					
B366670	42M	Angina/death secondary to ventricular fibrillation	2M	DDI/HOCarbamide	History of hypercholesterolemia, smoker. Treatment history: D4T/3TC/IDV, discontinued due to increased triglyceride and cholesterol
A95405	31M	Atrial Fibrillation/Atrial Flutter		AZT/3TC/NFV	No significant past medical history. Reverted to normal sinus rhythm after discontinuation of ABC
A95460	7 M	Tachycardia			Overdose ABC
B368720	69F	Cardiomyopathy/Dyspnea	10W	DDI/D4T/Antidepressants	Improved after d/c of ABC
A91515	50F	Exacerbate cardiomyopathy	27w		History of aortic valve replacement, arrhythmia
A96125A	44F	Ventricular fibrillation, sudden death, HSR	7W	3TC/ZDV	HSR at Wk7, including shoulder, chest pain, hypotension, CPK1100, AST646, ALT247; 7days post discontinue of ABC: ventricular fibrillation/cardiac arrest/thrombus in left anterior descending coronary artery
B374984A	40 M	MI	11M	IDV/EFV	History of smoker, family history of MI (father, age 39)
A96641	56 M	MI	See Notes	NFV/d4T	History of hypertension: HSR post 1 dose of ABC (discontinued); MI 4 months later
A89790	40-49M	Palpitations, left-sided chest pain	1 dose	ZDV/3TC	No further details
A86697	34M	Palpitations	1 day	Not stated	ABC continued, palpitations resolved 1 wk later
B378038A	35M	MI, death	2.5m	RTV+NVP	14m post-start RTV. Non-smoker, no family history of CV disease

* Excludes cases from Protocol CNAAB3005 and cases of myocardial infarction included in Table E below.

Table E: Myocardial Infarctions in Abacavir Recipients Captured in IND studies (Annual Report: 2 May 98 – 1 May 99)^{a,b}

Case #	Age/ Sex	Adverse Event	Onset Post-ABC	Concomitant Medications	Notes
Study CNA 3008					
A0067760	53 M	MI	2w	SQV/RTV/D4T	History of chronic lung disease, smoking; coronary artery disease, left anterior descending artery lesion treated with angioplasty
A0081817	54 M	MI	16w	Not stated	History of cardiomyopathy/congestive heart failure
A0074187	36M	MI	9w	EFV/IDV/d4T	History of hypertension, smoker
A0086790	59M	MI	8w	NFV/EFV/d4T	History of diabetes; prior treatment: RTV/SQV
A0073877	42 M	MI	58w	NVP/EFV/RTV/IDV	History of smoking
A0070659	46 M	MI, Pneumonia, fever, shortness of breath, chest pain	5w	Not stated	ABC continued
A0077902	44 M	MI	1y	Not stated	History of diabetes, smoking, drug abuse, high cholesterol
A0074502	40 M	MI/rash on upper back	19w	NFV/NVP	History of smoker, mild obesity, deep vein thrombosis
A0081056	60 M	MI/death	55w	IDV/ZDV/3TC	Subclavian steal
Study CNAB3008					
B0064934	49M	MI/ventricular fibrillation/tetraplegia	13w	DDI/HU/EFV	History of stress, smoking
B0057301	32 F	MI/nausea and vomiting	1w	RTV/SQV/NVP/Combivir™	History of smoking, "recidivant pneumonia" Note: ART history extensive, ambiguous
B0058448	33 F	MI	?	RTV/SQV/NVP/Combivir™	History of smoking, coronary artery disease, prior MI
B0061816	41M	MI	3m	IDV/RTV/NFV/3TC/ddI/d4t	History of smoking; had increased cholesterol, triglycerides
Study CNAB3004					
B0061871	53m	MI	6w	3TC/EFV/d4T	History of coronary heart disease, hypertension, recent MI; patient may have previously received ABC as study medication
Study CNAB3001					
A0081056		MI			No further details
Study CNA 2002					
B0059932	53m	MI	25m?	ZDV/3TC, then 3TC/NFV/d4t	Angina 4 weeks prior to MI
Study CNAB3003					
B0062717	55m	MI	13m	AZT/3TC	History of cardiovascular disease, peripheral vascular disease., previous MI

a. Other cardiac events (angina, congestive heart failure, arrhythmia, cardiac arrest, etc) omitted

b. Cases from Protocol CNAAB3005 are also excluded.

Appendix F

The following are the outstanding phase 4 commitments contained in the accelerated approval letter:

- Completion and submission of reports of the ongoing carcinogenicity studies.
- Conduction of a labeling comprehension study for subjects reading the Medication Guide and Warning Card.
- Proposal for study of the biologic mechanism/immunologic basis of hypersensitivity reactions to abacavir sulfate.
- The safety and efficacy of abacavir used in combination with other antiretroviral agents.
- The role of abacavir sulfate in therapy-experienced patients.
- The available information on the management of rash developing in patients who are being treated with multiple antiretroviral agents (including protease inhibitors and non-nucleoside reverse transcriptase inhibitors) and other commonly used drugs (e.g. Trimethoprim/sulfamethoxazole) that may cause rash.
- Evaluation of pharmacokinetics of abacavir in:
 1. Neonates
 2. Adults with hepatic impairment
 3. Adolescent patients
- Inclusion with the submission for traditional approval of abacavir an evaluation of safety, efficacy, and pharmacokinetics of abacavir in women and minorities.
- Completion and submission of the results of resistance and cross-resistance assessments from ongoing clinical studies

**DOCUMENT COMPLETE
PAGES NUMBERED INCORRECTLY**

/s/

Ekopimo Ibia
12/12/00 11:35:00 AM
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Therese Cvetkovich
12/15/00 12:26:53 PM
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Heidi M. Jolson
1/5/01 08:42:09 AM
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MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA # 20, 977, Serial number 000 Reviewer: LALJI MISHRA, Ph.D

NDA #20, 978, Serial number 000

Date Submitted: 12/16/99

Date Received: 12/17/ 99

Date Assigned: 01/18/00

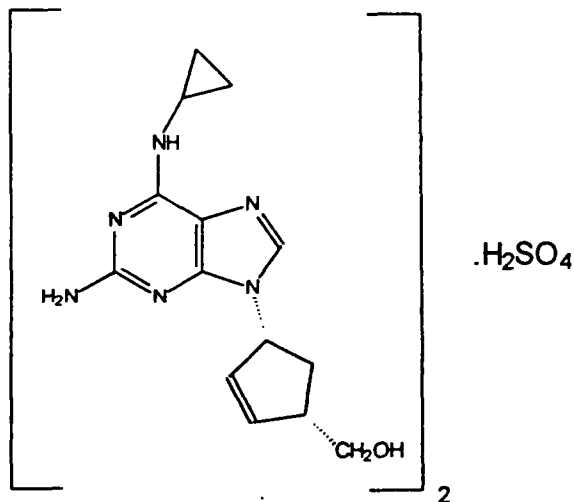
Date Completed: 06/06/00

Sponsor: Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Product Name(s):

- a. Proprietary: Ziagen TM
- b. Non-proprietary: Abacavir sulfate
- c. Chemical: [(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-2-cyclopenten-1-yl]methanol

Structural Formula:



Route of Administration/Dosage Form: Oral/Tablet

Indication: Treatment of HIV-1 infection

Supporting Documents: IND 45331

BACKGROUND

Abacavir sulfate (abacavir) is a synthetic carbocyclic nucleoside analogue that inhibits HIV-1 reverse transcriptase activity. Abacavir has been demonstrated to exhibit anti-HIV-1 activity both in vitro and in vivo. Glaxo-Welcome, Inc. has filed supplemental NDAs 20, 977 & 20, 978 to provide results from clinical studies in order to update the package insert. Abacavir first received approval for marketing on December 17, 1998 under accelerated approval regulations.

In the current application, Glaxo-Welcome, Inc. has submitted results of two studies; CNAAB3005 (a 48 week study comparing ABC/3TC/ZDV versus IDV/3TC/ZDV) and CNAAB 1012 (methadone/abacavir interaction study). Study CNAAB3005 provides data addressing equivalence of abacavir/lamivudine/zidovudine and indinavir/lamivudine/zidovudine (sNDA, vol. 1, page 77). For the detailed agency interpretation of these data, please see the Medical Officer's review. Study CNAAB 1012 deals with the interaction of methadone and abavavir. For the detailed agency interpretation of these data, please see the Biopharmaceutical/Pharmacokinetics review. Microbiology data of the study CNAAB3005 pertaining to genotypic and phenotypic resistance are reviewed here.

SUMMARY

Study CNAAB3005: Genotypic and Phenotypic Analysis of HIV-1 Reverse Transcriptase and Protease in HIV-1 Infected, Antiretroviral Naïve Adult Subjects Over 48 weeks of Therapy with ABC/3TC/ZDV or IDV/3TC/ZDV (Report No. RR 1990/00070/00).

Objectives

Primary

To compare the long-term safety and efficacy of abacavir sulfate (ABC)/lamivudine (3TC)/zidovudine (ZDV) versus indinavir (IDV)/3TC/ZDV over a period of 48 weeks.

Secondary

To measure the development of viral resistance (genotypic and phenotypic) in patients that do not achieve or maintain plasma HIV-1 RNA ≤ 400 copies/mL.

Study Design

CNAAB3005 was designed as a randomized, double-blind, multicenter study to evaluate the antiviral effect and durability of response (as measured by plasma HIV-1 RNA) and safety of ABC/3TC/ZDV versus IDV/3TC/ZDV in antiretroviral therapy naïve HIV-1 infected adults. Approximately 275 patients in each treatment group were enrolled for 48

weeks. In this study, patients were stratified by their screening plasma HIV-1 RNA level ($\geq 10,000$ -100,000 copies/mL, or $>100,000$ copies/mL) and randomly assigned to one of two treatment arms: 3TC/ZDV combination tablet (150 mg/300 mg BID) + ABC (300 mg BID) + IDV placebo or 3TC/ZDV combination tablet (150 mg/300 mg BID) + IDV (800 mg q8h) + ABC placebo. A secondary objective of this study was to measure the development of viral resistance to therapy. Both genotypic and phenotypic analyses were attempted in plasma samples from all patients who either failed to reach or rebounded to a pre-defined viral load (plasma HIV-1 RNA >400 copies/mL) after 16-48 weeks of therapy). Randomly selected samples from patients who were determined to be "virologic successes" (HIV-1 RNA ≤ 400 copies/mL) were examined for comparison purposes.

I. Pre-and Post-therapy Viral Load

The median baseline plasma HIV-1 RNA ranged from 4.3 to 6.6 $\log_{10}$ copies/mL for patients with virologic failure in the ABC/3TC/ZDV arm (n=32) and 4.2 to 5.7 $\log_{10}$ copies/mL for patients with virologic failure in IDV/3TC/ZDV arm (n=27). At the time of last genotypic analysis (week 16-48), the median plasma HIV-1 RNA ranged from 2.6-5.9 $\log_{10}$ copies/mL for patients in ABC/3TC/ZDV arm (n=27) and 2.6 to 5.5 $\log_{10}$ copies/mL for patients in IDV/3TC/ZDV group (n=20).

II. Genotypic Analysis

II (a) Protease Mutations:

IDV/3TC/ZDV arm

The protease mutations detected in HIV-1 isolates at baseline and after therapy week 12-44 weeks of IDV/3TC/ZDV therapy are shown in Table 1. Data presented in Table 1 are derived from APPENDIX A (vol. 52.4, sNDA 20, 977). Protease genotypes of baseline HIV-1 isolates were available from 16 patients. Patients who failed therapy had plasma HIV-1 RNA >400 c/mL. Matched baseline and on-therapy genotypes of HIV-1 isolates were available from 14 patients.

Table 1: Protease Genotypes of HIV-1 isolates from patients receiving IDV/3TC/ZDV and failing therapy (plasma HIV-1 RNA >400 c/mL)

	WT	M36I	L63P	A71V/T	V77I
Baseline (n=16)	1/16	3/16	9/16	4/16	7/16
On-therapy (n=14)	1/14	1/14	9/14	4/14	6/14

As shown in Table 1, most of the amino acids changes detected (M36I, M46I/L, L63P, A71T, V77I) were natural polymorphisms in the protease gene (Kozol *et al.*, 1996). These natural polymorphic mutations were also detected in baseline HIV-1 isolates from patients who were successful on IDV/3TC/ZDV therapy (plasma RNA $\log_{10}$ copies/mL ≤ 400 c/mL) (sNDA, vol. 52.4, page 19). The mutation M46I/L was detected in early isolates from 3/14 patients on IDV/3TC/ZDV therapy, but changed to wild type in subsequent isolates from the same patients. Additionally, isolates from most patients contained polymorphism at more than one amino acid position in the HIV-1 protease (sNDA, vol. 52.4, page 18).

ABC/3TC/ZDV arm

Table 2 shows mutations observed in baseline and on-therapy isolates from patients failing ABC/ 3TC/ZDV therapy (HIV-1 plasma RNA >400 c/mL). Data shown in Table 2 are derived from APPENDIX A (vol. 52.4, sNDA) and include only those patients for whom genotypes of matched baseline and on-therapy HIV-1 isolates were available. Protease genotype of matched baseline and on-therapy HIV-1 isolates were available from 20 patients. Most of the amino acid changes observed in baseline and on-therapy isolates were natural polymorphisms known to occur in the HIV-1 protease gene.

Table 2: Protease Genotypes of HIV-1 isolates from patients receiving ABC/ 3TC/ZDV and failing therapy (plasma HIV-1 RNA >400 c/mL)

	WT	M36I	L63P	A71V/T	V77I
Baseline (n=20)	7/20	1/20	8/20	0/20	3/20
On-therapy (n=20)	5/20	0/20	9/20	1/20	2/20

II (b) RT Mutations:

IDV/3TC/ZDV arm

The RT genotype of baseline isolates from patients receiving IDV/3TC/ZDV therapy was that of wild type except for the isolates from two patients. A baseline isolate from one patient had the T215Y/C mutation, and the isolate from the other patient harbored A98S/A mutation in the RT gene (sNDA 20-977, APPENDIX A, page 18). The RT genotype of HIV-1 isolates obtained during IDV/3TC/ZDV therapy are shown in Table 3. Only those patient for whom genotype of matched baseline HIV-1 isolates were available are included in Table 3, and the data is derived from APPENDIX A. The T215Y mutation persisted in isolates obtained at week 40 weeks of IDV/3TC/ZDV therapy (Table 3). However, the mutation A98S persisted only up to 12 weeks of IDV/3TC/ZDV therapy (sNDA 20-977, vol. 52.4, page 18).

Table 3: RT Genotypes of HIV-1 isolates from patients failing IDV/3TC/ZDV therapy (plasma HIV-1 RNA >400 c/mL)

	WT	M184V	M184V+ T215Y	T69D
IDV/3TC/ZDV (n=18)	9/18	8/18	1/18	1/18

Table 3 shows that M184V was the major RT mutation detected in HIV-1 isolates from 18 patients (9/18) receiving IDV/3TC/ZDV therapy by weeks 16-48. In addition, an on-therapy isolate from one patient contained the T69D mutation in the RT gene. The M184V mutation is associated with phenotypic resistance to 3TC, abacavir, didanosine, and T69D to zalcitabine.

ABC/3TC/ZDV arm

Baseline isolates from 20/21 patients receiving ABC/3TC/ZDV therapy had wild type RT genotype (sNDA 20-977, vol. 52.4, page 19). However, the baseline isolate from one patient harbored RT mutations I50V, and L210F/L. The significance of I50V or L210F/L mutation is not known. The RT genotypes of HIV-1 isolates obtained during ABC/3TC/ZDV therapy are shown in Table 4. Only those patient's for whom the genotypes of matched baseline isolates were available are included in Table 4. Data for table 4 is derived from APPENDIX A (sNDA, vol. 52.4, pages 19-20). These patients had plasma HIV-1 RNA > 400 c/mL at the time of treatment failure.

Table 4: RT Genotypes of HIV-1 isolates from patients failing ABC/3TC/ZDV therapy (HIV-1 plasma RNA >400 c/mL)

	WT	M184V	Y115F/Y M184V	M184V T215T/Y	M184V, ZDV* Resistant Mutations	I50V
ABC/3TC /ZDV (n=21)	4/21	11/21	1/21	1/21	3/21	1/21

*ZDV mutations: M41L, D67N, K70R, T215Y, and K219Q/E

As shown in Table 4, the M184V mutation was detected in HIV-1 isolates from 16/21 patients receiving ABC/3TC/ZDV therapy by weeks 12-48. The M184V mutation appeared alone or in combination with abacavir-associated mutation (Y115F) and/or ZDV (M41L, D67N, K70R, T215Y, and K219Q/E) in patients receiving ABC/3TC/ZDV combination therapy. Since abacavir also induces the M184V mutation, it appears that the preponderance of the M184V mutation in HIV-1 isolates from patients receiving ABC/3TC/ZDV combination therapy could be due to cumulative actions of

abacavir and 3TC. The I50V mutation persisted in isolates at weeks 16 and 24 from a patient receiving ABC/3TC/ZDV therapy. The significance of I50V mutation alone or in combination with other RT mutations is not known.

III. Phenotypic Analysis

III (a) Phenotypic analysis of baseline isolates:

Matched baseline isolates from antiretroviral therapy naïve patients randomized to receive either IDV/3TC/ZDV (n=13) or ABC/3TC/ZDV (n=10) therapy were susceptible to NRTIs (ABC, 3TC, ZDV, d4T, ddI) and PIs (indinavir, nelfinavir, ritonavir, saquinavir, and amprenavir) tested (sNDA 20-977, vol. 52.4, pages 21-22).

III (b) Phenotypic analysis of on-therapy isolates from patients failing IDV/3TC/ZDV or ABC/3TC/ZDV therapy:

IDV/3TC/ZDV arm

Phenotypic analysis data for on-therapy HIV-1 isolates were available from 13 patients. Only those patients for whom drug susceptibility data for matched baseline HIV-1 isolates were available are included in Table 5. Data presented in Table 5 are derived from APPENDIX B and C (sNDA, vol. 52.4, pages 21 and 25). These patients failed therapy and had plasma HIV-1 RNA level >400 c/mL. Resistance to 3TC (25 to 101-fold decrease in susceptibility) was observed for isolates from 6/13 patients after 16-48 weeks of therapy. The viral load, genotype at the time of phenotypic testing and drug susceptibility patterns for isolates from these 6/13 patients are shown in Table 5. These isolates were susceptible to the other NRTIs (abacavir, d4T, ZDV, ddI), and/or to protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, and amprenavir) tested. Similarly, on-therapy isolates from the remaining 7/13 patients were susceptible to 3TC and above-mentioned NRTIs and PIs.

Table 5: Susceptibility of HIV-1 isolates from patients failing IDV/3TC/ZDV therapy to 3TC, correlation with viral load and genotype

Patient #	HIV-1 RNA log ₁₀ copies/mL (wk 0)	HIV-1 RNA log ₁₀ copies/mL last generated (wk)	Genotype at week	Fold resistance to 3TC
5446	4.64	4.03 (wk 24)	M184V (wk 24)	25
5456	4.93	3.94 (wk 48)	M184V (wk 48)	39
5485	NA	NA	NA (wk 48)	25
5649	5.15	4.56 (wk 20)	M184V (wk 16)	88
6145	4.83	3.26 (wk 16)	M184V (wk16)	101
8155	5.04	3.49 (wk 36)	M184V (wk 24)	88

NA = Not available

ABC/3TC/ZDV arm

Data on the drug susceptibility of on-therapy HIV-1 isolates with matched baseline isolates resistance profile were available from 10 patients failing ABC/3TC/ZDV therapy. These patients had plasma HIV-1 RNA of >400 c/mL. HIV-1 isolates from 7/10 patients exhibited a 25 to 86-fold decrease in susceptibility to 3TC by week 16-48 of treatment. The viral load, genotype at the time of phenotypic testing and drug susceptibility patterns are shown in Table 6, and these data are derived from APPENDIX B and C (sNDA pages 22 and 25). These HIV-1 isolates harbored either M184V mutation alone or M184V mutation in combination with ABC or ZDV resistance associated-mutations. Of these 7 patients, HIV-1 isolates from 2 patients showed a 7 to 10-fold decrease in susceptibility to abacavir. These isolates harbored abacavir-associated mutations (Y115F/Y and M184V) and ZDV-associated mutations. HIV-1 isolates from these 7/10 patients were susceptible to other NRTIS (d4T, ddI, ZDV), and PIs (indinavir, nelfinavir, ritonavir, saquinavir, and amprenavir) tested. Similarly, isolates from the remaining 3/10 patients were susceptible to 3TC, ABC, d4T, ddI, ZDV and above-mentioned PIs.

Table 6: Susceptibility of HIV-1 isolates from patients failing ABC/3TC/ZDV therapy to 3TC, abacavir, and correlation with viral load and genotype

Patient #	HIV-1 RNA log ₁₀ Copies/mL (wk 0)	HIV-1 RNA log ₁₀ copies/mL last generated (wk)	Genotype at wk	Fold resistance to 3TC	Fold resistance to abacavir
5293	4.82	4.50 (wk 48)	M184V (wk48)	25	Susceptible
5589	4.70	4.47 (wk 40)	M184V (wk40)	25	Susceptible
5846	4.94	NA (wk 44)	M184V (wk 44)	25	Susceptible
5851	5.16	3.61 (wk 48)	Y115F/Y, M184V, T215T/Y (wk 48)	25	10
6074	4.69	2.83 (wk 28)	M184V (wk 28)	25	Susceptible
6392	4.31	4.61 (wk 20)	M184V (wk 16)	86	Susceptible
8199	5.66	2.91 (wk 40)	M814V, D67N, K70R, K219E/K (wk 40)	50	7

exhibited decreased susceptibility to both abacavir and 3TC. These isolates harbored M184V, Y115 F and T215Y mutations or M184V and other ZDV-associated mutations.

The viral load in patients failing ABC/3TC/ZDV therapy ranged from 2.6 to 5.79 log₁₀ c/mL. Although, there was no direct correlation of viral load increase with the emergence of M184V mutation, the preponderance of M184V mutation in isolates from patients failing ABC/3TC/ZDV suggested that the M184V mutation contributed towards the loss of drug activity. Other factors such as poor regimen adherence, and sub-optimum plasma levels of drug may have also contributed to decrease in drug activity.

REFERENCES

Hertogs, K., de Bethune, M-P., Miller, V., Ivens, T., Schel, P., Cauwenberge, A.V., Eynde, C.V.D., Gerwen, V.V., Azijn, H., Houtte, M.V., Peeters, F., Staszewski, S., Conant, M., Bloor, S., Kemp, S., Larder, B., and Pauwels, R. A rapid method for simultaneous detection of phenotypic resistance to inhibitors of protease and reverse transcriptase in recombinant human immunodeficiency virus type 1 isolates from patients treated with antiretroviral drugs. *Antimicrob. Agents and Chemother.* 1998; 42: 269-276.

Kozal, M.J., Shah, N., Shen, N., Yang, R., Fucini, R., Merigan, T.C., Richman, D.D., Morris, D., Hubbell, E., Chee, M., and Gingeras, T.R. Extensive polymorphisms observed in HIV-1 clade B protease gene using high-density oligonucleotide arrays. *Nature Medicine.* 1996; 2: 753-759.

Lanier, E.R. and Melby, T. Genotypic and phenotypic analysis of HIV-1 reverse transcriptase and protease in HIV-1 infected, antiretroviral naïve adult subjects over 48 weeks of therapy with ABC/3TC/ZDV or IDV/3TC/ZDV (GW Report No. RR 1990/00070/00).

ABACAVIR LABEL

The recommended changes to the approved label are in bold face.

MICROBIOLOGY

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate. Carbovir triphosphate is an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated.

Antiviral Activity In Vitro: The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIIB, a monocyte/macrophage tropic laboratory strain HIV-1 BaL and clinical isolates in lymphoblastic cell lines, primary monocytes/macrophages, and peripheral blood mononuclear cells, respectively. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM against HIV-1 IIIB, and was $0.26 \pm 0.18 \mu M$ ($1 \mu M = 0.28 \text{ mcg/mL}$) against eight clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from 0.07 to 1.0 μM . Abacavir had synergistic activity in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine in vitro. Most of these drug combinations have not been adequately studied in vivo. The relationship between in vitro susceptibility of HIV to abacavir and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV-1 isolates with reduced sensitivity to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from abacavir-treated patients showed point mutations in the reverse transcriptase gene that resulted in amino acid substitutions at positions K65R, L74V, Y115F, and M184V. Phenotypic analysis of HIV-1 isolates that harbored abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir in vitro.

Genetic analysis of HIV-1 isolates from 21 prior antiretroviral therapy naïve patients receiving abacavir/lamivudine/zidovudine combination therapy for 16-48 weeks showed that isolates from 15/21 patients harbored the M184V mutation either alone or in combination with abacavir and ZDV-associated mutations. Similarly, phenotypic analysis of HIV-1 isolates from 10 patients showed that isolates from 7 patients exhibited a 25 to 86 fold decrease in susceptibility to lamivudine in vitro. In addition, HIV-1 isolates from 2 of these 7 patients exhibited a 7 to 10-fold decrease in susceptibility to abacavir in vitro. The clinical relevance of genotypic and phenotypic changes associated with abacavir therapy is under evaluation.

Cross-Resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. Recombinant laboratory strains of HIV-1 (HXB2) containing multiple RT mutations conferring abacavir resistance exhibited cross-resistance to lamivudine, didanosine and zalcitabine in vitro.

RECOMMENDATIONS

Please incorporate the proposed changes in the Microbiology section of label to reflect new relevant drug resistance information.

(S)

Microbiologist

CONCURRENCES:

HFD-530/Dep Dir	<u>(S)</u>	Signature	<u>6/27/00</u>	Date
HFD-530/S micro	<u> </u>	Signature	<u> </u>	Date
CC:				

HFD-530/Original NDA (20-977)
 HFD-530/ Division File
 HFD-530/S Micro
 HFD-530/Review Micro
 HFD-530/CSO, Truffa, M.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 29, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Therese Cvetkovich, M.D., Medical Team Leader, DAVDP eso 10/27/00

NDA: 20-977 and 20-978 Ziagen (abacavir sulfate) Tablets and Oral Solution

Subject: Abacavir hypersensitivity reactions: a request for additional information.

Comments:

Please note that we do not believe that the incidence of abacavir hypersensitivity is increasing. Rather, we believe that, as information from an increasing number of studies, as well as from larger studies, becomes available, the incidence rate of abacavir hypersensitivity derived from clinical trials becomes increasingly accurate.

We appreciate your effort to resolve differences in the rate of hypersensitivity reactions in clinical trials as identified by GW and by FDA. However, we are dependent upon your provision of accurate numbers of patients exposed to abacavir in clinical trials. In our calculations we utilized as denominators the numbers of patients exposed to abacavir in clinical trials that you have provided in various submissions. We note that in the revised table that you provided the numbers of patients exposed to abacavir were increased in six studies, but that no change in the numbers of cases of hypersensitivity were identified. We would appreciate the chance to further review any updated information that you may have to support the rates of hypersensitivity in each trial. In addition, we believe it would be appropriate at this time to review all the ongoing clinical studies that you are conducting in which abacavir is used, and that would provide data to support an accurate estimation of the rate of hypersensitivity reactions caused by abacavir.

Therefore, we request the following:

1. Listing of all studies (completed and ongoing) conducted by GW in which a significant number of patients are exposed to abacavir. For example, studies conducted under other IND's (such as amprenavir or GW433908) in which most patients receive abacavir as background therapy could provide useful information.

2. Compilation of and submission of all SAE reports from each study, as well as current numbers and durations of patients exposed to abacavir.

We recognize that it is unlikely that these data can be submitted, analyzed, and reflected in the abacavir label currently under review. Therefore, as an alternative to changing the overall rate of hypersensitivity reactions, we request that the rate of abacavir hypersensitivity reactions identified in study 3005 be represented in this label.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

cc:

Original NDA 20-977 and 20-978

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 9, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Imo Ibia, M.D., Medical Officer, DAVDP eso 8/8/00
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP eso 8/9/00 tc

NDA: 20-977 and 20-978 Ziagen (abacavir sulfate) Tablets and Oral Solution

Subject: Request for additional information for Supplemental NDA (S-002) dated December 16, 1999.

- One of the class C disease progressors listed (Volume 14 Page 70) was identified as subject number 6611 (diagnosis: unconfirmed Cytomegalovirus disease). We could find no documentation for a subject with this ID number. In addition, subject number 7243 (diagnosis: cutaneous Kaposi sarcoma) was listed in the case narratives and case report forms but was not included in the list of subjects who died or progressed to Class C (Volume 14 page 70). Please confirm the appropriate documentation for each of these subjects.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

cc:
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 12, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Andrei Breazna, Ph.D., Statistical Reviewer, DAVDP 3-6-00

NDA: 20-977 and 20-978 Ziagen (abacavir sulfate) Tablets and Oral Solution

Subject: Request for additional information concerning the December 16, 1999 supplemental application (24 and 48 week data from CNAAB3005).

1. Please provide a dataset structured like PCRMARCH, but with the virological failures (coded by them "Confirmed Failure") only at week 48. If a patient had a "K-M" virological failure early in the trial, but no treatment switches, protocol violations, etc. by week 48 and has the RNA reading under 400 c/mL at week 48, that would be a success; readings of the RNA level over 400 c/mL at week 48 would be considered failures at that time. The dataset should allow for the user to perform a 48 week Intent-to-treat analysis under the non-completer=failure clause.
2. Please provide a K-M dataset (with the K-M definition of virological failure) that is not truncated at 48 weeks, but has all the available data.
3. Please provide a clarification of the STRATA definition.

Should you have any questions or need clarification of the above requests, we are available for a telephone conference.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Melissa M. Truffa, R.Ph.
Regulatory Project Manager, DAVDP
Division of Antiviral Drug Products



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 20, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Ekopimo Ibia, M.D., Medical Officer, DAVDP
John Martin, M.D., Medical Officer, DAVDP

NDA: 20-977 and 20-978 Ziagen (abacavir sulfate) Tablets and Oral Solution

Subject: Efficacy supplement dated December 16, 1999.

Comment:

- Please submit a table summarizing by treatment group the clinical laboratory abnormalities for all grades (Grade 1-4).

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Original NDA 20-977 and 20-978
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: April 20, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Ekopimo Ibia, M.D., Medical Officer, DAVDP 4/14/00 eso EI
John Martin, M.D., Medical Officer, DAVDP eso 4/20/00 JM

NDA: 20-977 and 20-978 Ziagen (abacavir sulfate) Tablets and Oral Solution

Subject: Efficacy supplement dated December 16, 1999.

Comments:

1. Please submit the Case Report Forms for all Grade 3 and 4 elevations of CK (or CPK).
2. Table 1 below is the summary of the outcome of randomized treatment at Week 48 in the ITT population (missing = failure). From analysis of the SAS dataset titled 'Pcmmarch.xpt' submitted March 24, 2000 at the request of the review team, there appears to be discrepancies between your original submission and the reanalysis of this new dataset in the ITT population (missing = failure) as shown on Table 2. Please provide an explanation for the discrepancies noted.

Table 1

	ABC/3TC/ZDV N=282	IDV/3TC/ZDV N=280	Total N=562
Plasma HIV-1 RNA $\leq$ 400 copies/mL	133 (47)	136 (49)	269 (48)
Plasma HIV-1 RNA >400 copies/mL ^a	36 (13)	23 (8)	59 (10)
Discontinued due to adverse event	43 (15)	55 (20)	98 (17)
Discontinued due to other reasons ^b	48 (17)	48 (17)	96 (17)
Randomized but did not start treatment	20 (7)	15 (5)	35 (6)
Data not available at Week 48	2 (<1)	3 (1)	5 (<1)

a. Includes discontinuations due to virologic failure at or before Week 48.

b. Consent withdrawal, lost to follow-up, protocol violation, changed ART, and other

Table 2

	ABC/3TC/ZDV ^a N=282	ABC/3TC/ZDV ^b N=262	IDV/3TC/ZDV ^a N=280	IDV/3TC/ZDV ^b N=265
Plasma HIV-1 RNA <400 copies/mL	133 (47)	129	136 (49)	132
Plasma HIV-1 RNA >400 copies/mL	36 (13)	35	23 (8)	31
Discontinued due to adverse event	43 (15)	25	55 (20)	32
Discontinued due to other reasons ^c	48 (17)	30	48 (17)	30
Randomized but did not start treatment	20 (7)	-	15 (5)	-
Data not available at Week 48	2 (<1)	-	3 (1)	-
Confirmed Failure	-	43	-	40

^a Applicant's summary of outcome of randomized treatment at Week 48 ITT population (missing = failure).

^b Reanalysis from SAS dataset 'pcrmarch.xpt'

^c Includes Class C disease progression, consent withdrawn, lost to follow up, protocol violation, changed ART, met protocol defined switch criterion, never below 400 copies/mL, no RNA sample, and other.

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Original NDA 20-977 and 20-978
Division File
HFD-530/CSO/Truffa



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 14, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Andrei Breazna, Ph.D., Statistical Reviewer, DAVDP 3-6-00

NDA: 20-977 and 20-978 Ziagen (abacavir sulfate) Tablets and Oral Solution

Subject: Request for additional information concerning the December 16, 1999 supplemental application (24 and 48 week data from CNAAB3005).

Please provide a dataset (1 observation per patient) with the following variables:

1. SUBJECT
2. INVID
3. INVNAME
4. TRTCD
5. TRTNAME
6. RNA2
7. RNA4
8. RNA8
9. RNA12
10. RNA16
11. RNA20
12. RNA24
13. RNA28
14. RNA32
15. RNA36
16. RNA40
17. RNA44
18. RNA48
19. TIME (day of failure or last day observed)
20. FAIL (0 if patient did not fail treatment, 1 if a failure occurred)
21. REASON (explanation of failure like protocol violation, withdrawal of consent, AE, AIDS defining event, etc.)

Please note that RNAX is the HIV-1RNA measurement at week X.
In addition please provide the SAS programs used to produce the dataset.

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Melissa M. Truffa, R.Ph.
Regulatory Project Manager, DAVDP
Division of Antiviral Drug Products

cc:
Original NDA 20-977 and 20-978
Division File
HFD-530/CSO/Truffa

**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: October 12, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Therese Cvetkovich, M.D., Medical Team Leader, DAVDP eso 10-12-00

NDA: 20-977 and 20-978 Ziagen (abacavir sulfate) Tablets and Oral Solution

Subject: FDA summary of abacavir hypersensitivity reactions (HSR) in controlled trials.

We are providing the following table in response to your question about our rationale for changing the overall rate of hypersensitivity identified in clinical trials from 5% to 6% in the abacavir label. The overall rate increased due to the impact of the high rate of hypersensitivity identified in study 3005 (the largest study to date). While the table identifies slightly different numbers of cases from each study compared with your analysis, we continue to have confidence in our identification of cases. Therefore, we believe that the label should reflect the overall rate based our case identification, as was done with the initial approved abacavir label.

Study Number	Number receiving abacavir	HSR cases identified by applicant	HSR cases identified by FDA	Rate % (FDA Analysis)
2001	79	3	3	3.8
2002	60	3	4	6.7
2003	32	0	0	0.0
2004	78	4	4	5.1
3001	48	2	3	6.3
3002	91	3	5	5.5
3003	85	4	5	5.9
3006	100	2	3	3.0
3005	262	19	20	7.6
Total	835	40	47	5.6

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