CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

Trade Name: Ziagen

Generic Name: (abacavir sulfate)

Sponsor: GlaxoSmithKline

Approval Date: August 2, 2004

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APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-977/S-012
NDA 20-978/S-014

GlaxoSmithKline
Attention: Martha Anne A. Moore, R.Ph.
Antiviral/Antibacterial US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to your supplemental new drug applications dated October 2, 2003, received October 3, 2004, 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:

October 30, 2003	June 08, 2004	July 06, 2004
November 14, 2003	June 14, 2004 (2)	July 08, 2004
January 19, 2004	June 16, 2004	July 14, 2004
February 27, 2004	June 17, 2004	July 22, 2004
March 02, 2004	June 24, 2004	July 29, 2004
April 19, 2004	June 25, 2004 (2)	July 30, 3004
April 30, 2004	June 30, 2004 (3)	August 2, 2004.
May 07, 2004	July 02, 2004	

Specifically, these supplemental new drug applications provide for the use of ZIAGEN® (abacavir sulfate, 600 mg) tablets and oral solution once daily in combination with other antiretroviral agents for the treatment of HIV-1 infection.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide and text for the Warning Card). Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-977/S-012 and NDA 20-978/S-014." Approval of these submissions by FDA is not required before the labeling is used.

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. We are waiving the pediatric study requirement for ages less than three months and deferring pediatric studies for ages three months to 17 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing pediatric study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 3 months to 17 years.

   Final Report Submission: December 31, 2007.

   Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated **"Required Pediatric Study Commitments"**.

In addition, we remind you of your postmarketing study commitments in your submission dated July 27, 2004, which are listed below.

2. Provide human pharmacokinetic information on plasma abacavir concentrations and intracellular carbovir triphosphate [CBV-TP] concentrations following administration of abacavir 600mg once daily. Provide this information from collaborative study COL101665 following successful completion of quality assurance activity. Alternatively, if study COL101665 can not be delivered, provide this human pharmacokinetic information from a new study.

   Timeline: If study COL101665 is completed, submit to FDA no later than March 31, 2005. If a new study must be done, this new study report should be submitted to FDA within 24 months of receiving feedback from FDA on the proposed study design.

2. Assess baseline and failure RT resistance mutations and failure phenotypes of HIV-1 isolates from patients who experience virologic failure in clinical study CAL30001, a study comparing 600 mg once daily abacavir vs. 300 mg twice daily abacavir (in combination with other drugs). Submit an analysis of genotypic and phenotypic results of study CAL30001.

   Timeline: Submit results of these assessments within 12 months of the date of this letter.

3. Assess the frequency and severity of hypersensitivity to abacavir (given 600mg once daily or 300mg twice daily) in combination with other antiretroviral drugs in study ESS101822. This

randomized, open-label, multicenter, parallel group study is designed to assess 900 abacavir-naive patients.

Timeline: Submit the results within 18 months of the date of this letter.

4. Provide additional safety information from GSK-sponsored clinical trials utilizing abacavir plus stavudine (with other antiretroviral drugs). Specifically, provide a report of 96-week results of study ESS40001 (an open-label, randomized study comparing the safety and efficacy of ABC/d4T/3TC versus ABC/3TC/EFV versus ABC/3TC/908/RTV in therapy-naive patients) and a summary of deaths, dropouts, and serious adverse events from other GSK-sponsored clinical studies utilizing abacavir plus stavudine.

   Timeline: Submit results by February 28, 2005.

5. Determine the *in vitro* combination antiretroviral activity relationships of abacavir with tenofovir, abacavir with efavirenz, and abacavir with emtricitabine.

   Timeline: Results for ABC/TDF, ABC/EFV and ABC/FTC will be submitted to FDA by November 30 2004.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol"**, **"Postmarketing Study Final Report"**, or **"Postmarketing Study Correspondence."**

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact Tanima Sinha, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

{See appended electronic signature page}

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

Enclosure: Approved Draft Labeling (Package Insert, Medication Guide and Warning Card)

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

/s/

Debra Birnkrant
8/2/04 12:44:32 PM
NDA 20-977, 20-978

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

LABELING

PRESCRIBING INFORMATION

ZIAGEN®
(abacavir sulfate)
Tablets

ZIAGEN®
(abacavir sulfate)
Oral Solution

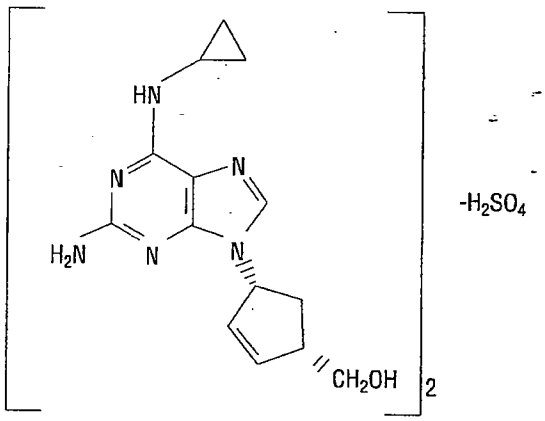
WARNINGS

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible.
Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
Reintroduction of ZIAGEN or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours (see WARNINGS and PRECAUTIONS: Information for Patients).

Lactic Acidosis and Severe Hepatomegaly: 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).

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 *(1S,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 *1S, 4R* 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 as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

ZIAGEN Oral Solution is for oral administration. Each milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg/mL) as active ingredient and the following inactive ingredients: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

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

MICROBIOLOGY

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted intracellularly by cellular enzymes to the active metabolite, carbovir triphosphate, 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. Abacavir is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Antiviral Activity: The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The IC_{50} values of abacavir against different HIV-1

clades (A-E) ranged from 0.0015 to 1.0 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic activity in vitro in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin had no effect on the in vitro anti-HIV-1 activity of abacavir.

Resistance: HIV-1 isolates with reduced susceptibility to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from patients failing an abacavir-containing regimen demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V in HIV-1 RT contributed to abacavir resistance. In a study of therapy-naive adults receiving ZIAGEN 600 mg once daily (n = 384) or 300 mg twice daily (n = 386), in a background regimen of lamivudine 300 mg once daily and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure at 48 weeks was similar between the 2 groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT mutations that emerged during abacavir once-daily and twice-daily therapy were K65R, L74V, Y115F, and M184V/I. The mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median-fold decrease of 1.3 (range 0.5 to 11) compared with 29% (5/17) of the failure isolates in the twice-daily arm with a median-fold decrease of 0.92 (range 0.7 to 13).

Cross-Resistance: Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Recombinant laboratory strains of HIV-1_{HXB2} containing multiple abacavir resistance-associated mutations, namely, K65R, L74V, M184V, and Y115F, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in vitro. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

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 1,200 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 ± SD) and $AUC_{(0\text{-}12\ hr)}$ was 6.02 ± 1.73 mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{max} was 4.26 ± 1.19 mcg/mL

(mean ± SD) and AUC_∞ was 11.95 ± 2.51 mcg•hr/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 $AUC_{(0\text{-}6\ hr)}$ to plasma abacavir $AUC_{(0\text{-}6\ hr)}$ 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/kg (mean ± 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.

Adults with Impaired Hepatic Function: The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. A dose of 200 mg (provided by 10 mL of ZIAGEN Oral Solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.

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

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

Gender: A population pharmacokinetic analysis in HIV-infected male (n = 304) and female (n = 67) patients showed no gender differences in abacavir AUC normalized for lean body weight.
Race: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics.
Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Due to the common metabolic pathways of abacavir and zidovudine via glucuronyl transferase, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.
Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each patient received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC_{∞} and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

Methadone: In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently 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.

INDICATIONS AND USAGE

ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.
Additional important information on the use of ZIAGEN for treatment of HIV-1 infection:

- ZIAGEN is one of multiple products containing abacavir. Before starting ZIAGEN, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir.
- In one controlled study (CNA30021), more patients taking ZIAGEN 600 mg once daily had severe hypersensitivity reactions than patients taking ZIAGEN 300 mg twice daily. (See WARNINGS, ADVERSE REACTIONS, and Description of Clinical Studies.)

Description of Clinical Studies: ***Therapy-Naive Adults:*** **CNA30024** was a multicenter, double-blind, controlled study in which 649 HIV-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) or zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and

efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Study participants were: male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years, the median pretreatment CD4+ cell count was 264 cells/mm^3, and median plasma HIV-1 RNA was 4.79 $\log_{10}$ copies/mL. The outcomes of randomized treatment are provided in Table 1.

Table 1. Outcomes of Randomized Treatment Through Week 48 (CNA30024)

Outcome	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Responder*	*69% (73%)*	*69% (71%)*
Virologic failures†	6%	4%
Discontinued due to adverse reactions	14%	16%
Discontinued due to other reasons‡	10%	11%

*Patients achieved and maintained confirmed HIV-1 RNA ≤50 copies/mL (<400 copies/mL) through Week 48 (Roche® AMPLICOR Ultrasensitive HIV-1 MONITOR standard test 1.0 PCR).
†Includes viral rebound, insufficient viral response according to the investigator, and failure to achieve confirmed ≤50 copies/mL by Week 48.
‡Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells/mm^3 in the group receiving ZIAGEN and 155 cells/mm^3 in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C events and 3 deaths) and 5 subjects (2%) on the zidovudine arm (3 CDC classification C events and 2 deaths) experienced clinical disease progression.

CNA3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults with a pre-entry plasma HIV-1 RNA >10,000 copies/mL were randomized to receive either ZIAGEN (300 mg twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. Study participants were male (87%), Caucasian (73%), black (15%), and Hispanic (9%). At baseline the median age was 36 years, the median baseline CD4+ cell count was 360 cells/mm^3, and median baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL through 48 weeks of treatment are summarized in Table 2.

Table 2. Outcomes of Randomized Treatment Through Week 48 (CNA3005)

Outcome	ZIAGEN plus Lamivudine/Zidovudine (n = 282)	Indinavir plus Lamivudine/Zidovudine (n = 280)
HIV-1 RNA <400 copies/mL	46%	47%
HIV-1 RNA ≥400 copies/mL*	29%	28%
Discontinued due to adverse reactions	10%	13%
Discontinued due to other reasons†	8%	8%
Randomized but never initiated treatment	7%	5%

* Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48 (Roche Amplicor HIV-1 MONITOR Test).
† Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, clinical progression, and other.

Through Week 48, an overall mean increase in CD4+ cell count of about 150 cells/mm^3 was observed in both treatment arms.

CNA30021 was an international, multicenter, double-blind, controlled study in which 770 HIV-infected, therapy-naive adults were randomized and received either abacavir 600 mg once daily or abacavir 300 mg twice daily, both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily. The double-blind treatment duration was at least 48 weeks. Study participants had a mean age of 37 years, were: male (81%), Caucasian (54%), black (27%), and American Hispanic (15%). The median baseline CD4+ cell count was 262 cells/mm^3 (range 21 to 918 cells/mm^3) and the median baseline plasma HIV-1 RNA was 4.89 $\log_{10}$ copies/mL (range: 2.60 to 6.99 $\log_{10}$ copies/mL).

The outcomes of randomized treatment are provided in Table 3.

Table 3. Outcomes of Randomized Treatment Through Week 48 (CNA30021)

Outcome	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Responder*	64% (71%)	65% (72%)
Virologic failure†	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons‡	11%	13%

*Patients achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL) through week 48 (Roche AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version 1.0).
†Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by Week 48, and insufficient viral load response.
‡Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells/mm^3 in the group receiving abacavir 600 mg once daily and 200 cells/mm^3 in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving

ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subjects (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression. None of the deaths were attributed to study medications.

CONTRAINDICATIONS

ZIAGEN Tablets and Oral Solution are contraindicated in patients with previously demonstrated hypersensitivity to abacavir or any other component of the products (see WARNINGS). Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product. Fatal rechallenge reactions have been associated with readministration of abacavir to patients with a prior history of a hypersensitivity reaction to abacavir (see WARNINGS and PRECAUTIONS).

ZIAGEN Tablets and Oral Solution are contraindicated in patients with moderate or severe hepatic impairment.

WARNINGS

Hypersensitivity Reaction: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN and other abacavir-containing products. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Important information on signs and symptoms of hypersensitivity, as well as clinical management, is presented below.

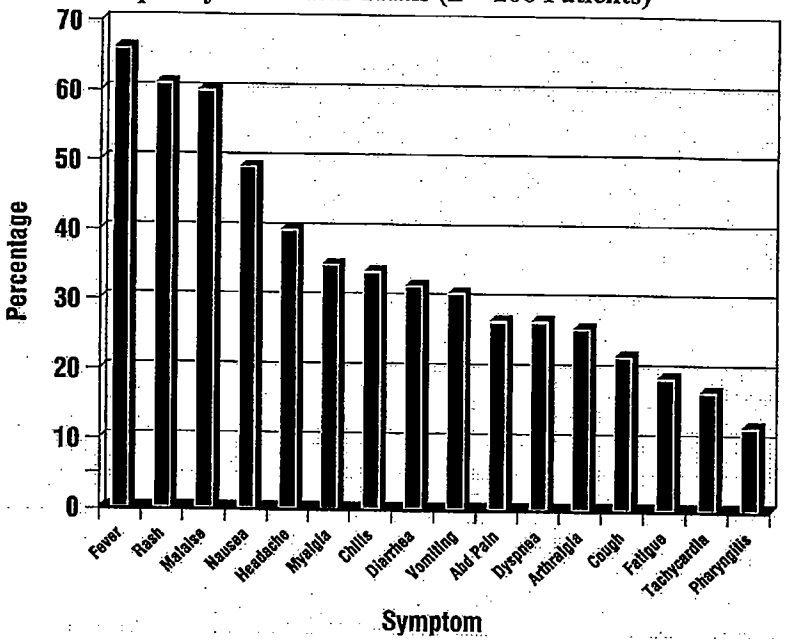
Signs and Symptoms of Hypersensitivity: Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups.

Group 1: Fever
Group 2: Rash
Group 3: Gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain)
Group 4: Constitutional (including generalized malaise, fatigue, or achiness)
Group 5: Respiratory (including dyspnea, cough, or pharyngitis).

Hypersensitivity to abacavir following the presentation of a single sign or symptom has been reported infrequently.

Hypersensitivity to abacavir was reported in approximately 8% of 2,670 patients (n = 206) in 9 clinical trials (range: 2% to 9%) with enrollment from November 1999 to February 2002. Data on time to onset and symptoms of suspected hypersensitivity were collected on a detailed data collection module. The frequencies of symptoms are shown in Figure 1. Symptoms usually appeared within the first 6 weeks of treatment with abacavir, although the reaction may occur at any time during therapy. Median time to onset was 9 days; 89% appeared within the first 6 weeks; 95% of patients reported symptoms from 2 or more of the 5 groups listed above.

Figure 1: Hypersensitivity-Related Symptoms Reported with ≥10% Frequency in Clinical Trials (n = 206 Patients)



Other less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray findings (predominantly infiltrates, which can be localized), and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions. In one study, 4 patients (11%) receiving ZIAGEN 600 mg once daily experienced hypotension with a hypersensitivity reaction compared with 0 patients receiving ZIAGEN 300 mg twice daily.

Physical findings associated with hypersensitivity to abacavir in some patients include lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and rash. The rash usually appears maculopapular or urticarial, but may be variable in appearance. There have been reports of erythema multiforme. Hypersensitivity reactions have occurred without rash.

Laboratory abnormalities associated with hypersensitivity to abacavir in some patients include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.

Clinical Management of Hypersensitivity: **Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. To minimize the risk of a life-threatening hypersensitivity reaction, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**

When therapy with ZIAGEN has been discontinued for reasons other than symptoms of a hypersensitivity reaction, and if reinitiation of ZIAGEN or any other abacavir-containing product is under consideration, carefully evaluate the reason for discontinuation of ZIAGEN to ensure that the patient did not have symptoms of a hypersensitivity reaction. If hypersensitivity cannot be ruled out, DO NOT reintroduce ZIAGEN or any other abacavir-containing product. If symptoms consistent with

hypersensitivity are not identified, reintroduction can be undertaken with continued monitoring for symptoms of a hypersensitivity reaction. Make patients aware that a hypersensitivity reaction can occur with reintroduction of ZIAGEN or any other abacavir-containing product and that reintroduction of ZIAGEN or any other abacavir-containing product needs to be undertaken only if medical care can be readily accessed by the patient or others.

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 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).

Fat Redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients: ***Hypersensitivity Reaction:*** Inform patients:

- **that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of ZIAGEN, and encourage the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about ZIAGEN. (The complete text of the Medication Guide is reprinted at the end of this document.)**
- **to carry the Warning Card with them.**
- how to identify a hypersensitivity reaction (see WARNINGS and MEDICATION GUIDE).
- that if they develop symptoms consistent with a hypersensitivity reaction to discontinue treatment with ZIAGEN and seek medical evaluation immediately.
- that a hypersensitivity reaction can worsen and lead to hospitalization or death if ZIAGEN is not immediately discontinued.

- that in one study, more severe hypersensitivity reactions were seen when ZIAGEN was dosed 600 mg once daily.
- **to not restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.**
- that a hypersensitivity reaction is usually reversible if it is detected promptly and ZIAGEN is stopped right away.
- that if they have interrupted ZIAGEN for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart ZIAGEN or any other abacavir-containing product without medical consultation and that restarting abacavir needs to be undertaken only if medical care can be readily accessed by the patient or others.

General: Inform patients that some HIV medicines, including ZIAGEN, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly).
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. Advise patients 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.
Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known 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 patients receiving methadone-maintenance therapy (40 mg and 90 mg daily) with 600 mg of ZIAGEN twice daily (twice the currently 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 was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

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. 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 a dose approximately 8 times the human exposure at the recommended 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. Fetal malformations (increased incidences of fetal anasarca and skeletal malformations) and developmental toxicity (depressed fetal body weight and reduced crown-rump length) were observed in rats at a dose which produced 35 times the human exposure, based on AUC. Embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) and toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at half of the above-mentioned dose in separate fertility studies conducted in rats. In the rabbit, no developmental toxicity and no increases in fetal malformations occurred at doses that produced 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 dosed twice daily have been established in pediatric patients 3 months to 13 years of age. 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). The safety and effectiveness dosed once daily in pediatric patients have not been established.
CNA3006 was a randomized, double-blind study comparing ZIAGEN 8 mg/kg twice daily plus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m^2 twice daily versus lamivudine 4 mg/kg twice daily plus zidovudine 180 mg/m^2 twice daily. Two hundred and five therapy-experienced pediatric patients were enrolled: female (56%), Caucasian (17%), black (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 $\log_{10}$ 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. At 16 weeks the proportion of patients responding based on plasma HIV-1 RNA ≤400 copies/mL was significantly higher in patients receiving ZIAGEN plus lamivudine plus zidovudine compared with patients receiving lamivudine plus zidovudine, 13% versus

2%, respectively. Median plasma HIV-1 RNA changes from baseline were -0.53 $\log_{10}$ copies/mL in the group receiving ZIAGEN plus lamivudine plus zidovudine compared with -0.21 $\log_{10}$ copies/mL in the group receiving lamivudine plus zidovudine. Median CD4+ cell count increases from baseline were 69 cells/mm^3 in the group receiving ZIAGEN plus lamivudine plus zidovudine and 9 cells/mm^3 in the group receiving lamivudine plus zidovudine.

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: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). In one study, once-daily dosing of ZIAGEN was associated with more severe hypersensitivity reactions (see WARNINGS and PRECAUTIONS: Information for Patients).

Therapy-Naive Adults: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 4.

Table 4. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA30024*) Through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Dreams/sleep disorders	10%	10%
Drug hypersensitivity	9%	<1%†
Headaches/migraine	7%	11%
Nausea	7%	11%
Fatigue/malaise	7%	10%
Diarrhea	7%	6%
Rashes	6%	12%
Abdominal pain/gastritis/ gastrointestinal signs and symptoms	6%	8%
Depressive disorders	6%	6%
Dizziness	6%	6%
Musculoskeletal pain	6%	5%
Bronchitis	4%	5%
Vomiting	2%	9%

*This study used double-blind ascertainment of suspected hypersensitivity reactions. During the blinded portion of the study, suspected hypersensitivity to abacavir was reported by investigators in 9% of 324 patients in the abacavir group and 3% of 325 patients in the zidovudine group.

[†]Ten (3%) cases of suspected drug hypersensitivity were reclassified as not being due to abacavir following unblinding.

Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥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 CNA3005 are listed in Table 5.

Table 5. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Naive Adults (CNA3005) Through 48 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine/Zidovudine (n = 262)	Indinavir plus Lamivudine/Zidovudine (n = 264)
Nausea	19%	17%
Headache	13%	9%
Malaise and fatigue	12%	12%
Nausea and vomiting	10%	10%
Diarrhea	7%	5%
Fever and/or chills	6%	3%
Depressive disorders	6%	4%
Musculoskeletal pain	5%	7%
Skin rashes	5%	4%
Ear/nose/throat infections	5%	4%
Viral respiratory infections	5%	5%
Anxiety	5%	3%
Renal sign/symptoms	<1%	5%
Pain (non-site-specific)	<1%	5%

Five patients receiving ZIAGEN in Study CNA3005 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.

ZIAGEN Once Daily versus ZIAGEN Twice Daily (Study CNA30021): Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a ≥5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily from Study CNA30021 were similar. (For hypersensitivity reactions, patients receiving ZIAGEN once daily showed a rate of 9% in comparison to a rate of 7% for patients receiving ZIAGEN twice daily.) However, patients receiving ZIAGEN 600 mg once daily, experienced a significantly higher incidence of severe drug hypersensitivity reactions and severe diarrhea compared to patients who received ZIAGEN 300 mg twice daily. Five percent (5%) of patients receiving ZIAGEN 600 mg once daily had severe drug hypersensitivity reactions compared to 2% of patients receiving ZIAGEN 300 mg twice daily. Two percent (2%) of patients receiving ZIAGEN 600 mg once daily had severe diarrhea while none of the patients receiving ZIAGEN 300 mg twice daily had this event.

Therapy-Experienced Pediatric Patients: Treatment-emergent clinical adverse reactions (rated by the investigator as moderate or severe) with a ≥5% frequency during therapy with ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m^2 twice daily compared

with lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily from CNA3006 are listed in Table 6.

Table 6. Treatment-Emergent (All Causality) Adverse Reactions of at Least Moderate Intensity (Grades 2-4, ≥5% Frequency) in Therapy-Experienced Pediatric Patients (CNA3006) Through 16 Weeks of Treatment

Adverse Reaction	ZIAGEN plus Lamivudine plus Zidovudine (n = 102)	Lamivudine plus Zidovudine (n = 103)
Fever and/or chills	9%	7%
Nausea and vomiting	9%	2%
Skin rashes	7%	1%
Ear/nose/throat infections	5%	1%
Pneumonia	4%	5%
Headache	1%	5%

Laboratory Abnormalities: Laboratory abnormalities (Grades 3-4) in therapy-naive adults during therapy with ZIAGEN 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily compared with zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg daily from CNA30024 are listed in Table 7.

Table 7. Laboratory Abnormalities (Grades 3-4) in Therapy-Naive Adults (CNA30024) Through 48 Weeks of Treatment

Grade 3/4 Laboratory Abnormalities	ZIAGEN plus Lamivudine plus Efavirenz (n = 324)	Zidovudine plus Lamivudine plus Efavirenz (n = 325)
Elevated CPK (>4 X ULN)	8%	8%
Elevated ALT (>5 X ULN)	6%	6%
Elevated AST (>5 X ULN)	6%	5%
Hypertriglyceridemia (>750 mg/dL)	6%	5%
Hyperamylasemia (>2 X ULN)	4%	5%
Neutropenia (ANC <750/mm^3)	2%	4%
Anemia (Hgb ≤6.9 gm/dL)	<1%	2%
Thrombocytopenia (P1t <50,000/mm^3)	1%	<1%
Leukopenia (WBC≤1,500/mm^3)	<1%	2%

In another study of therapy-naive adults (CNA3005), hyperglycemia and disorders of lipid metabolism occurred with similar frequency in patients treated with ZIAGEN and patients treated with indinavir. In a study of therapy-experienced pediatric patients (CNA3006), laboratory abnormalities (anemia, neutropenia, liver function test abnormalities, and CPK elevations) were observed with similar frequencies as in a study of therapy-naive adults (CNA30024). Mild elevations of blood glucose were more frequent in pediatric patients receiving ZIAGEN (CNA3006) as compared to adult patients (CNA30024).

The frequencies of treatment-emergent laboratory abnormalities were comparable between treatment groups in Study CNA30021.

Other Adverse Events: In addition to adverse reactions in Tables 4, 5, 6, and 7, other adverse events observed in the expanded access program were pancreatitis and increased GGT.
Observed During Clinical Practice: In addition to adverse reactions reported from clinical trials, the following events have been identified during use of abacavir in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to abacavir, or a combination of these factors.
Body as a Whole: Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).
Hepatic: Lactic acidosis and hepatic steatosis (see WARNINGS and PRECAUTIONS).
Skin: Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases. There have also been reports of erythema multiforme with abacavir use.

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.**
ZIAGEN may be taken with or without food.
Adults: The recommended oral dose of ZIAGEN for adults is 600 mg daily, administered as either 300 mg twice daily or 600 mg once daily, in combination with other antiretroviral agents.
Adolescents and Pediatric Patients: The recommended oral dose of ZIAGEN for adolescents and pediatric patients 3 months to up to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.
Dose Adjustment in Hepatic Impairment: The recommended dose of ZIAGEN in patients with mild hepatic impairment (Child-Pugh score 5 to 6) is 200 mg twice daily. To enable dose reduction, ZIAGEN Oral Solution (10 mL twice daily) should be used for the treatment of these patients. The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate to severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.

HOW SUPPLIED

ZIAGEN is available as tablets and oral solution.
ZIAGEN Tablets: Each tablet contains abacavir sulfate equivalent to 300 mg abacavir. The tablets are yellow, biconvex, capsule-shaped, film-coated, and imprinted with "GX 623" on one side with no marking on the reverse side. They are packaged as follows: Bottles of 60 tablets (NDC 0173-0661-01). Unit dose blister packs of 60 tablets (NDC 0173-0661-00). Each pack contains 6 blister cards of 10 tablets each.
Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP).

ZIAGEN Oral Solution: It is a clear to opalescent, yellowish, strawberry-banana-flavored liquid. Each mL of the solution contains abacavir sulfate equivalent to 20 mg of abacavir. It is packaged in plastic bottles as follows: Bottles of 240 mL (NDC 0173-0664-00) with child-resistant closure. This product does not require reconstitution.
Store at controlled room temperature of 20° to 25°C (68° to 77°F) (see USP). DO NOT FREEZE. May be refrigerated.

ANIMAL TOXICOLOGY

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined.

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Research Triangle Park, NC 27709

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MEDICATION GUIDE

ZIAGEN® (ZY-uh-jen) Tablets
ZIAGEN® Oral Solution
Generic name: abacavir (uh-BACK-ah-veer) sulfate tablets and oral solution

Read the Medication Guide that comes with Ziagen before you start taking it and each time you get a refill because there may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Be sure to carry your Ziagen Warning Card with you at all times.

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

- **Serious Allergic Reaction to Abacavir.** Ziagen contains abacavir (also contained in Epzicom™ and Trizivir®). Patients taking Ziagen may have a serious allergic reaction (hypersensitivity reaction) that can cause death. **If you get a symptom from 2 or more of the following groups while taking Ziagen, stop taking Ziagen and call your doctor right away.**

	Symptom(s)
Group 1	**Fever**
Group 2	**Rash**
Group 3	**Nausea, vomiting, diarrhea, abdominal (stomach area) pain**
Group 4	**Generally ill feeling, extreme tiredness, or achiness**
Group 5	**Shortness of breath, cough, sore throat**

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

If you stop Ziagen because of an allergic reaction, NEVER take Ziagen (abacavir sulfate) or any other abacavir-containing medicine (Epzicom and Trizivir®) again. If you take Ziagen or any other abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get **life-threatening symptoms** that may include **very low blood pressure** or **death.**

If you stop Ziagen for any other reason, even for a few days and you are not allergic to Ziagen, talk with your doctor before taking it again. Taking Ziagen again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before. If your doctor tells you that you can take Ziagen again, **start taking it when you are around medical help or people who can call a doctor if you need one.**

- **Lactic Acidosis. Some HIV medicines, including Ziagen, can cause a rare but serious condition called lactic acidosis with liver enlargement (hepatomegaly).** Nausea and tiredness that don't get better may be symptoms of lactic acidosis. In some cases this condition can cause death. Women, overweight people, and people who have taken HIV medicines like Ziagen for a long time have a higher chance of getting lactic acidosis and liver enlargement. Lactic acidosis is a medical emergency and must be treated in the hospital.

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

What is Ziagen?

Ziagen is a prescription medicine used to treat HIV infection. Ziagen is taken by mouth as a tablet or a strawberry-banana-flavored liquid. Ziagen is a medicine called a nucleoside analogue reverse transcriptase inhibitor (NRTI). Ziagen is always used with other anti-HIV medicines. When used in combination with these other medicines, Ziagen helps lower the amount of HIV found in your blood. This helps to keep your immune system as healthy as possible so that it can help fight infection.

Different combinations of medicines are used to treat HIV infection. You and your doctor should discuss which combination of medicines is best for you.

- **Ziagen does not cure HIV infection or AIDS.** We do not know if Ziagen will help you live longer or have fewer of the medical problems that people get with HIV or AIDS. It is very important that you see your doctor regularly while you are taking Ziagen.
- **Ziagen does not lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others, it is important to always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Ziagen has not been studied in children under 3 months of age or in adults over 65 years of age.

Who should not take Ziagen?

Do not take Ziagen if you:

- **have ever had a serious allergic reaction (a hypersensitivity reaction) to Ziagen or any other medicine that has abacavir as one of its ingredients (Epzicom and Trizivir).** See the end of this Medication Guide for a complete list of ingredients in Ziagen. If you have had such a reaction, return all of your unused Ziagen to your doctor or pharmacist.
- **have a liver that does not function properly.**

Before starting Ziagen, tell your doctor about all your medical conditions, including if you:

- **are pregnant or planning to become pregnant.** We do not know if Ziagen will harm your unborn child. You and your doctor will need to decide if Ziagen is right for you. If you use Ziagen while you are pregnant, talk to your doctor about how you can be on the Antiviral Pregnancy Registry for Ziagen.
- **are breastfeeding.** We do not know if Ziagen can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

- **methadone**
- **Epzicom (abacavir sulfate and lamivudine) and Trizivir (abacavir sulfate, lamivudine, and zidovudine).**

How should I take Ziagen?

- **Take Ziagen by mouth exactly as your doctor prescribes it.** Your doctor will tell you the right dose to take. The usual doses are 1 tablet twice a day or 2 tablets once a day. Do not skip doses.
- **You can take Ziagen with or without food.**
- **If you miss a dose of Ziagen, take the missed dose right away. Then, take the next dose at the usual time.**
- **Do not let your Ziagen run out.**
- **Starting Ziagen again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.** If you run out of Ziagen even for a few days, you must ask your doctor if you can start Ziagen again. If your doctor tells you that you can take Ziagen again, start taking it when you are around medical help or people who can call a doctor if you need one.
- If you stop your anti-HIV drugs, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat.
- **If you take too much Ziagen, call your doctor or poison control center right away.**

What should I avoid while taking Ziagen?

- Do not take Epzicom **(abacavir sulfate and lamivudine)** or Trizivir **(abacavir sulfate, lamivudine, and zidovudine)** while taking Ziagen. Some of these medicines are already in Ziagen.

Avoid doing things that can spread HIV infection, as Ziagen does not stop you from passing the HIV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if Ziagen can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV should not breastfeed because HIV can be passed to the baby in the breast milk.

What are the possible side effects of Ziagen?

Ziagen can cause the following serious side effects:

- **Serious allergic reaction that can cause death.** (See "What is the most important information I should know about Ziagen?" at the beginning of this Medication Guide.)

- **Lactic acidosis with liver enlargement (hepatomegaly) that can cause death.** (See "What is the most important information I should know about Ziagen?" at the beginning of this Medication Guide.)
- **Changes in body fat.** These changes have happened in patients taking antiretroviral medicines like Ziagen. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects of Ziagen include nausea, vomiting, tiredness, headache, diarrhea, trouble sleeping, fever and chills, and loss of appetite. Most of these side effects did not cause people to stop taking Ziagen.

This list of side effects is not complete. Ask your doctor or pharmacist for more information.

How should I store Ziagen?

- Store Ziagen at room temperature, between 68° to 77°F (20° to 25°C). Do not freeze Ziagen.
- Return your unused Ziagen to your doctor or pharmacist for proper disposal.
- **Keep Ziagen and all medicines out of the reach of children.**

General information for safe and effective use of Ziagen

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Ziagen for a condition for which it was not prescribed. Do not give Ziagen to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Ziagen. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for the information that is written for healthcare professionals or call 1-888-825-5249.

What are the ingredients in Ziagen?

Tablets: Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film-coating is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

Oral Solution: Each milliliter (1 mL) of Ziagen Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg/mL) as active ingredient and the following inactive ingredients: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), sorbitol solution, and water.

GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709

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Date of Issue MG-

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

(Front of card)

WARNING CARD
ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

Patients taking Ziagen may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking Ziagen, stop taking Ziagen and call your doctor right away.

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, or abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, or sore throat

Always carry this Warning Card with you to help recognize symptoms of this allergic reaction.

(Back of Card)

WARNING CARD

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

If you must stop treatment with Ziagen because you have had an allergic reaction to abacavir, **NEVER** take Ziagen or another abacavir-containing medicine (Epzicom™ and Trizivir®) again. If you take Ziagen or another abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get **life-threatening symptoms** that may include **very low 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.

July 2004

RL-

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

MEDICAL REVIEW

CLINICAL REVIEW

Medical Officer's Review NDA 20-977/SE2-012 and 20-978/SE2-014

Date submitted:	October 2, 2003
Date Received:	October 3, 2003
Draft Review completed:	July 23, 2004
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PDUFA date:	August 3, 2004
Action date:	August 2, 2004
Reviewed by:	Andrea N. James, M.D. Medical Officer, HFD-530
Applicant:	GlaxoSmithKline P.O. Box 13398 Five Moore Drive Research Triangle Park North Carolina 27709-3398
Drug name:	Abacavir sulfate (ZIAGEN®, ABC)
Formulation:	300 mg tablets and 20 mg/mL base oral solution
Indication:	Treatment of HIV-1 infection

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Clinical Review for sNDA 20-977/S-12 and 20-978/S-14

Executive Summary

I. Recommendations

A. Recommendation on Approvability

A high rate of adherence to antiretroviral therapy (ART) is recognized as an important predictor of treatment success, and poor adherence is one of the primary reasons for therapy failure. Lower levels of adherence have been associated with the development of drug resistance, increased likelihood of virologic failure, and increased morbidity and mortality [Paterson, 2000; Carmona, 2000; Walsh, 2000]. There is some evidence that simplified regimens (specifically lower pill burden) are associated with improved adherence [Bartlett, 2001; Vibhagool, 2001].

Abacavir sulfate (abacavir, ABC, ZIAGEN™) tablets and solution dosed 300mg twice daily were granted accelerated approval on December 17, 1998 based on 16 – 24 week efficacy and safety data and then granted traditional approval on April 15, 2004 based on 48 week efficacy and safety data. Towards the goal of simplifying therapy, GlaxoSmithKline (GSK) undertook a clinical development program with the aim of providing a once daily option for ABC.

In October 2003, GSK submitted the data from CNA30021, a large, randomized, double-blind, active-controlled, Phase 3 study, which provides evidence of 600mg once daily ABC's efficacy in antiretroviral treatment (ART) naïve subjects. Specifically the combination of ABC 600 mg OAD plus lamivudine (3TC) and efavirenz (EFV) demonstrated efficacy that was non-inferior to the combination of ABC 300mg twice daily (BID) plus 3TC and EFV. The comparator regimen and the end-point analyses were considered appropriate for the populations being studied.

Study CNA30021 confirmed the risk of developing the serious and potentially life-threatening adverse event, hypersensitivity reaction (HSR), while using ABC. The HSR rate in CNA30021 (8% overall) was consistent with the HSR rate observed in CNA3005(8%) and CNA30024 (8%), which is slightly higher than the currently labeled rate of 5%. HSR is already described throughout the label including a boxed warning, however, based on the above data the label will be changed to reflect the more consistent HSR rate of 8%. Review of the safety data did identify a safety signal with ABC OAD, namely, an increased incidence of grade 3 and grade 4 ABC hypersensitivity reactions (HSR) (5% versus 2%, p = 0.017) and diarrhea (2% versus 0, p =

0.015) in the ABC OAD group in comparison to the ABC BID group. Although these safety risks are considered serious, especially the ABC HSR, DAVDP believes it is manageable through labeling changes that will highlight the increased incidence of severe ABC HSR and diarrhea and provide healthcare providers and patients with information on management of suspected ABC HSR. Another ABC HSR related safety signal was hypotension, which was seen in 11% of the subjects who experienced ABC HSR on the OAD arm compared to 0 subjects who experienced HSR on the ABC BID arm. Although the finding of ABC HSR associated hypotension was not statistically significant, it is a clinically significant finding that healthcare professionals need to be made aware of. Of note there were no deaths on study attributed to either these severe adverse events or ABC OAD. DAVDP believes that these safety risks do not outweigh the benefit of ABC OAD as a treatment option for HIV-1 infected patients.

The other safety data was consistent with known and expected events related to the use of antiretrovirals (ARV) in general or to HIV-1 disease itself.

In addition to CNA30021, GSK submitted one pharmacokinetic (PK) study, CNA10905, in support of this supplemental NDA (sNDA). CNA10905 did not contribute any efficacy data, and the safety data was minimal and the safety events were not unusual or unexpected.

From the clinical perspective, the 48 week efficacy and sNDA support the approval of once daily (OAD) dosing of ABC 600mg (dosage form 300mg tablet and solution) for the treatment of HIV-1 infection

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

DAVDP has made the following Phase 4 commitment requests of GSK:

1.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Product name: Abacavir sulfate (ABC, ZIAGEN®)
Class: Antiretroviral drug
Subclass: Nucleoside reverse transcriptase analogue (NRTI)
Route: Oral
Formulation: 300 mg tablet; 20mg/mL base solution

The data source for this review comes from the October 3, 2003 GSK submission. The submission includes data collected from one large pivotal clinical trial (Study CNA30021) and one supportive PK trial (Study CNA10905).

Study CNA30021 was designed as a randomized, double-blind, active-controlled study comparing the efficacy and safety of ABC (600mg once daily) versus ABC (300mg twice daily), as a component of triple drug therapy including 3TC (300mg once daily) and EFV (600mg once daily). Subjects were stratified prior to randomization based on screening HIV RNA viral load

(less than or greater than 100,000 copies/mL). Subjects were then randomized 1:1 to one of two treatment arms:

Arm 1: ABC 600mg OAD + ABC BID placebo + 3TC 300mg once daily + EFV 600mg once daily

Arm 2 : ABC 300mg BID + ABC OAD placebo + 3TC 300mg once daily + EFV 600mg once daily

The primary efficacy outcome was the proportion of subjects with a viral load of ≤ 50 copies/mL who sustained this response for the 48 week study period as defined by the time to loss of virologic response algorithm (TLOVR). A total of 784 subjects were enrolled into the study and randomized. A total of 384 subjects received at least one dose of ABC 600 mg OAD in study CNA30021.

Supportive study CNA10905 was a single dose PK study of ABC 300mg with PK assessments over a 24 hour period. No subjects received ABC 600mg OAD in this study.

B. Efficacy

For study CNA30021 all of the efficacy analyses conducted by the applicant and confirmed by the FDA clinical/statistical review team concluded that overall ABC OAD was non-inferior to ABC BID in treatment-naïve subjects when each treatment was given in combination with 3TC and EFV over a 48 week study period. The two arms had a similar number of virologic responders and virologic failures when evaluating the ITT population (all subjects randomized and exposed to at least one dose of any study medication), however, the reasons for non-virologic failures differed slightly between the two arms: the ABC OAD arm had slightly more subjects deemed failures due to discontinuations because of adverse events (13% vs 11%) while the ABC BID arm had more subjects deemed treatment failures due to discontinuations for reasons other than adverse events (13% vs 11%). Overall, based on the ITT population and the primary analysis of TLOVR there was no apparent difference in the response rates of the ABC OAD arm versus the ABC BID arm (64% and 65% respectively).

No statistically significant difference was seen between the unstratified groups for the primary endpoint of VL < 50 copies/mL in the ITT or As Treated group (all subjects with study data available while still taking their randomized treatment regimen). For study CNA30021 all of the efficacy analyses conducted by the applicant and confirmed by the FDA clinical/statistical review team concluded that overall ABC OAD was non-inferior to ABC BID when given in combination with 3TC and EFV over a 48 week study period in treatment-naïve subjects. The two groups had a similar number of virologic responder, treatment and study discontinuations, and virologic failures. While the ABC OAD group had slightly more discontinuations due to adverse events, the ABC BID group had slightly more discontinuations due to "other events". Additionally, the incidence of HIV-related disease progression was similar between the ABC OAD and ABC BID groups.

No statistically significant difference was seen between the unstratified groups for the primary endpoint of VL < 50 copies/mL in the ITT or As Treated group. However, in the As Treated population subgroup analysis the > 100,000 strata in the OAD group did not meet the predetermined non-inferiority delta margin of 12%. Given the smaller sample size and the fact that this is a subgroup analysis, it is difficult to draw any conclusions from these results. However, ABC's ability to provide durable antiviral activity in subjects with baseline viral loads of >100,000 has been a recurrent concern that as of yet well-controlled, clinical trials have not been able to answer. This disparity between the > 100,000 strata of the OAD and BID arms highlights this issue once again. Of note, the virologic failure rates in the > 100,000 strata of the OAD and BID arms were comparable thus making the suggestion of inferiority (based on the delta margin) in the OAD arm compared to the BID arm clinically irrelevant in this particular study.

In study CNA30021 the median changed in baseline CD4+ cell count on the ABC OAD arm was robust and equivalent to the median change in baseline CD4+ cell count observed on the ABC BID arm at Week 48 (ABC OAD, 188 cells/mm^3; ABC BID 200 cells/mm^3).

The NRTI-associated mutation, M184V/I (10/18 (56%) on the OAD arm; 8/20 (40%) on the BID arm), was the most commonly encountered resistance mutation in subjects who failed on either arm. The majority of subjects (>60%) who failed with M184V/I remained fully susceptible to ABC. The other 30+% of subjects had a greater than 2.5 fold shift in ABC susceptability. Other common treatment emergent resistance mutations were NRTI-associated mutation, L74V and NNRTI-associated, K103N.

C. Safety

Based on the 48-week data submitted in CNA30021, ABC OAD, in combination with other antiretrovirals, has a safety profile that is acceptable and in general similar to that of ABC BID. The incidences of AEs, treatment-emergent AEs, and severe or serious AEs were similar between the ABC OAD + 3TC + EFV and ABC BID + 3TC + EFV treatment groups with the following exception: the OAD arm had significantly more severe ABC HSR (19 (5%) versus 7 (2%)) and diarrhea (6 (2%) versus 0) AEs than the ABC BID arm. Additionally, hypotension was seen in 11% (n=4) of the subjects who experienced ABC HSR on the OAD arm compared to 0 of the subjects who experienced HSR on the ABC BID arm. Although the finding of ABC HSR associated hypotension on the OAD arm was not statistically significant, it is a clinically significant symptom associated with ABC HSR that healthcare professionals need to be made aware of.

HSR is the most serious of the listed and expected adverse events associated with ABC. In CNA30021, HSR was reported at a slightly higher rate (9% in the OAD arm, 7%) in the BID arm) than the labeled rate of 5%. This rate is consistent with rates of 8% observed in each of the two pivotal studies supporting traditional approval of ABC.

There is no evidence indicating ABC OAD contributed to any adverse clinical manifestations that have not been previously described for ABC BID. There were no fatalities attributable to either treatment regimen.

In general, the safety results demonstrated that both regimens were well tolerated, and safety profiles were comparable over 48 weeks of randomized treatment exposure.

D. Dosing

The pivotal study, CNA30021 support the new proposed dose of ABC 600mg given once daily as an effective and generally well tolerated dose in HIV-1 infected patients compared to the already approved ABC dose of 300mg twice daily .

GSK did not submit any new PK data that directly supports 600mg once daily dosing. However, study CNA10905 evaluated 24 hour PK of a single dose of 300mg in subjects who were at steady-state on a pre-existing regimen containing ABC 300mg BID. Although, study CNA10905 does not provide data specific to the 600mg once daily dose the results support clinical investigation of once daily dosing.

MO Comment: *Given that more subjects developed the M184V/I mutation (although not statistically significant) on ABC OAD versus ABC BID this reviewer believes that additional information on the PK of ABC 600mg OAD (particularly intracellular carbovir triphosphate levels) may provide useful information in determining whether or not drug levels are being maintained as well as with twice daily dosing and if not, whether this may be leading to increased NRTI resistance.*

E. Special Populations

CNA30021 had a diverse subject population with 19% female subjects and 46% non-white subjects on average. The data demonstrate that ABC OAD is no less effective than ABC BID in producing a clinical response and no more toxic in any subgroup of subjects on the basis of gender, race or ethnicity. The results of Dr. Smith's subgroup analysis for the primary efficacy endpoint based on age using the median age cutoff of 35 years did show a significantly inferior treatment response on the ABC OAD arm compared to the ABC BID arm in subjects $\leq$ 35 years of age.

MO Comment: *There is no obvious reason why younger subjects (namely, $\leq$ 35 years of age) would respond less well than older subjects to ABC OAD. The fact that overall the analysis of subjects on ABC OAD is non-inferior means that > 35 year old ABC OAD subjects did better than > 35 year old ABC BID subjects. This appears to be a chance statistical phenomenon that does not have any significant clinical impact.*

ABC is currently approved for use in children as young as 3 months old. ABC exists in a suspension specifically designed for use by children who cannot swallow tablets. No pediatric

data were submitted with this supplement. ABC OAD is currently not recommended for children.

[ ]

No data on subjects with renal or hepatic impairment were submitted with this supplement. Approximately 18% of the subjects in CNA30021 were co-infected with Hepatitis B or Hepatitis C or in less than 1% both Hepatitis B and C. The virologic response rate was lower in the co-infected subjects (ABC OAD arm, 62% and ABC BID arm, 57%) than in the non co-infected subjects (65% versus 67% respectively). However, the sample size was small and these subjects as part of the enrollment criteria had to have relatively normal liver enzymes and no evidence of clinically active hepatitis. All of the above makes it difficult to 1) draw any conclusion from these results and 2) to extrapolate these results to a population with active liver disease. Currently there is labeling for patients with hepatic insufficiency that recommends reducing the dose of ABC to 200mg bid in patients with mild hepatic impairment (Child Pugh's Class A). ABC use in subjects with moderate to severe hepatic impairment is not recommended. These recommendations are based on a single-dose PK study involving nine healthy subjects and nine subjects with mild hepatic impairment. The 9 subjects with mild hepatic impairment experienced an 89% mean increase in AUC and a 58% mean increase in half-life.

MO Comment: *ABC OAD is not indicated for subjects with any degree of hepatic insufficiency.*

Clinical Review

I. Introduction and Background

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

Abacavir sulfate (ABC, ZIAGEN®) is a synthetic carbocyclic nucleoside analogue. Based upon pharmacologic characteristics , the compound is classified as an inhibitor of the HIV-1 reverse transcriptase (RT) enzyme. As with other nucleoside RT inhibitors (NRTIs), ABC acts as a chain terminator of HIV-1 replication, thereby preventing conversion of viral ribonucleic acid (RNA) into proviral deoxyribonucleic acid (DNA). ABC has been developed by GSK for the treatment of HIV-1 infection. ABC 300mg given orally twice daily is indicated for the treatment of HIV infection in adults in combination with other antiretroviral drugs. Accelerated approval of ABC was granted on December 17, 1998 based upon 16 and 24 week results from studies CNAB3003, CNAA3006 and CNAB3005. The accelerated approval was granted contingent on GSK submitting the results of three 48-week studies of ABC's safety and efficacy to support traditional approval. At the time of accelerated approval two of these studies were already underway: CNAA3006, a 48-week study in therapy-experienced pediatric subjects and study CNAB3005, a 48-week non-inferiority study in treatment naïve adults. Since the time of accelerated approval GSK has submitted the 48-week results of CNAB3005 in the form of an efficacy supplement, which was reviewed, approved and the results incorporated into the ABC label, and the 48-week results of CNA300024 (a 48-week non-inferiority study in treatment naïve adults).

The pediatric study, CNAA3006, compared a triple nucleoside regimen (ABC + 3TC + ZDV) to a dual nucleoside regimen (3TC + ZDV), and was unblinded after Week 16. Although the study was carried out to 48 weeks, the data lack clinical relevance and robustness because of the unblinding and the comparator dual nucleoside arm, thus DAVDP released GSK from the Phase 4 commitment requiring submission of CNAA3006 results to support traditional approval. However, DAVDP requested that GSK submit the 48-week data from CNAA3006 and that they provide an updated summary of the clinical pharmacology, safety, and efficacy of abacavir in pediatric patients as a Phase 4 commitment for traditional approval.

GSK is now proposing a once daily dosing regimen of ABC 600mg.

B. State of Armamentarium for Indication(s)

There are now 21 drugs approved for the treatment of HIV-1 infection (this list does not include fixed dose combinations or different formulations). These drugs fall into four classes based on mechanism of action in the HIV life cycle: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and fusion/entry inhibitors (Table 1).

TABLE 1 Approved Antiretrovirals

Drug Class	Generic Name	Trade Name	Chemical Name
NRTI	zidovudine	Retrovir®	AZT
	didanosine	Videx®	ddI
	zalcitabine	Hivid®	ddC
	stavudine	Zerit®	d4T
	lamivudine	Epivir®	3TC
	abacavir	Ziagen®	
	tenofovir	Viread®	
	emtricitabine	Emtriva®	FTC
NNRTI	delavridine	Rescriptor®	
	nevirapine	Viramune®	
	efavirenz	Sustiva®	
PI	indinavir	Crixivan®	
	ritonavir	Norvir®	
	saquinavir, hard gel	Invirase®	
	saquinavir, soft gel	Fortavase®	
	nelfinavir	Viracept®	
	amprenavir	Agenerase®	
	fos-amprenavir	Lexiva®	
	atazanavir	Reyataz®	
	lopinavir/ritonavir fixed dose combination	Kaletra®	
Fusion/Entry Inhibitor	enfuvirtide	Fuzeon®	T20

According to the 2003 DHHS HIV-1 Treatment Guidelines "treatment goals should be maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality". Obstacles in achieving these goals include drug side effects, drug intolerance and drug resistance. Long-term tolerance, simple dosing schedules and more favorable resistance profiles are in demand, and have become the driving forces in antiretroviral drug development.

The pivotal study CNA30021 submitted in this supplement was designed to evaluate the safety and durable efficacy of ABC dosed once daily at 600mg.

C. Important Milestones in Product Development

ABC was initially investigated unde [redacted] mitted June 1, 1994. DAVDP allowed the initial Phase 1 single dose pharmacokinetic study in adults to proceed on June 24, 1994. Phase 2 studies were initiated in February 1995, and a phase 1 study in pediatrics was initiated in March 1995. The End-of-Phase 2 meeting was held in January 1997. DAVDP convened a closed session of the Antiviral Advisory Committee to discuss ABC's Phase 3 development plans. Phase 3 studies began in March 1997. The pre-NDA meeting was held in February 1998. The NDAs for the tablet (20-977) and the oral solution (20-978, (chemistry, manufacturing and control data only)) were submitted on June 24, 1998, and contained the16 – 24 week efficacy and safety data from 3 pivotal trials (CNAB3005, CNAA3006 and CNAB3003). The NDAs were presented at an open session of the Antiviral Advisory Committee on November 2, 1998. The Committee voted (7 for; 2 against) in favor of accelerated approval of ABC under the provisions of 21 CFR 314 Subpart H. The Committee recommended that the applicant commit to the widest possible dissemination of information about hypersensitivity reactions (HSR). Abacavir tablets (NDA 20-977) and oral solution (NDA 20-978) received accelerated approval based on 16 - 24 week efficacy and safety data on December 17, 1998.

GSK committed to use diligent efforts to complete studies of ABC's durable antiviral effects in order to provide those results in support of traditional approval as required under the accelerated approval regulations. GSK submitted an efficacy supplement providing 48 week durability data from CNAB3005 on December 16, 1999. This efficacy supplement was approved and the results incorporated into the label on December 15, 2000.

DAVDP and GSK agreed that GSK needed an additional confirmatory study of ABC's durability and long term safety to fulfill their commitment. DAVDP and GSK agreed at the pre-sNDA meeting held on March 13, 2003 that a 48-week non-inferiority study, CNA30024, fulfilled GSK's commitment in support of traditional approval and that an Antiviral Advisory Committee meeting was not needed for that sNDA. ABC received tradtional approval on April 15, 2004 based on the cumulative 48-week efficacy and safety data of CNA3005 and CNA30024.

D. Other Relevant Information

Since the 1998 approval in the United States, abacavir has been approved in 88 other countries worldwide. No applications for approval have been withdrawn or turned down. This supplemental NDA provides evidence of durable antiviral efficacy and long term safety of ABC at a new dose, 600mg once daily. This once daily dose is not approved in any other country at this time.

E. Important Issues with Pharmacologically Related Agents

Recently, two studies using the combination of ABC plus tenofovir (TDF) as part of a triple nucleoside regimen have had a disproportionate amount of virologic failures when compared to the control arm and to the antiviral response rates observed in other studies using a 3-drug antiretroviral regimen. Below is a synopsis of these two studies:

- ESS30009, a phase III, randomized, open label study of ABC/3TC fixed dose combination (FDC)+ TDF vs. ABC/3TC FDC +EFV. Virologic non-response was defined as at least one of the following:
  - failure to achieve a 2 log drop from baseline by Week 8.
  - a 1 log increase above nadir on any subsequent visit.

Of the subjects randomized to the ABC/3TC + TDF arm 50/102 (49%) met the definition of virologic non-response at Week 8. Of the subjects randomized to the ABC/3TC + EFV arm 5/92 (5.4%) met the definition of virologic non-response Week 8. Of the subjects randomized to the ABC/3TC FDC + TDF arm 30/63 (47.6%) met the definition of virologic non-response at Week 12. Of the subjects randomized to the ABC/3TC + EFV arm 3/62 (4.8%) met the definition of virologic non-response at Week 12. Genotypic analysis of the failures on the ABC/3TC FDC + TDF arm showed an M184V mutation alone in 13 subjects, and M184V + K65R mutations in 23 subjects. Based on these results the ABC/3TC FDC + TDF arm was terminated prematurely.

- Farthing, et al (2003) conducted a small pilot study to assess the efficacy of ABC/3TC FDC + TDF in ART naïve subjects. The virologic failure criteria were defined as either:
  - failure to achieve a 2 log drop from baseline by Week 8 or
  - a 1 log increase above nadir on any subsequent visit.

Twenty subjects enrolled, three subjects withdrew prematurely and nine subjects had baseline VL > 100,000. Nine of 17 subjects (52%) had viral load (VL) rebound (1 at Week 4; 6 at Week 8; 2 at Week 16). Genotypic analysis showed an M184V mutation alone in 5 subjects, M184V + K65R mutations in 4 subjects and wild-type in 2 subjects. The study was prematurely interrupted.

Investigations by both GSK and Gilead have yet to identify any specific pharmacologic interaction for these excessive failure rates. Specifically, each company has tested for and not found any intracellular antagonism between abacavir and tenofovir. Further investigations are needed to determine the cause of these virologic failures.

MO Comment: *Currently there is controversy regarding the use of any triple nucleoside regimen to treat HIV-1 infection because of a growing mass of data that demonstrate that triple nucleoside regimens are inferior in their ability to virologically suppress and maintain suppression as compared to NNRTI and PI based regimens . The 2003 DHHS guidelines have relegated the triple nucleoside regimen, Trizivir, to the position of "alternative regimen" to be used only if an NNRTI or PI based regimen can not be used or tolerated.*

Given the above results of ABC+3TC+TDF, the ABC/3TC FDC will be labeled to advise health care professionals and consumers against using this FDC in combination with any other NRTIs as part of a triple nucleoside regimen

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

There was no new chemistry or animal pharmacology/toxicology with this sNDA.

Information from Dr. Smith's Statistical Review confirming the efficacy endpoints in the clinical trials is incorporated into Section VI – Integrated Review of Efficacy. Please see Dr. Smith's Statistical Review for detailed efficacy analyses.

Please refer to Dr. Mishra's Microbiology review for a detailed analysis of the ABC resistance data submitted with this sNDA.

GSK provided genotypic and phenotypic analyses data on baseline and on-therapy isolates from subjects who experienced virologic failure enrolled in study CNA30021. Forty-four (44) subjects in the OAD treatment group and 41 subjects in the BID treatment group met protocol defined virologic failure. In addition, DAVDP requested that GSK provide genotypic and phenotypic analyses data on three additional subjects (Subjects 53385, 52643 and 51676), who discontinued treatment and had unsuppressed virus at the time of discontinuation, but did not meet the definition of virologic failure as per the TLOVR algorithm. For the purposes of this section alone "virologic failure" is the term used to refer to all subjects who provided resistance data.

Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT mutations that emerged during ABC OAD and ABC BID therapy were K65R, L74V, Y115F, and M184V/I. The mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).

Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once daily arm had a >2.5-fold decrease in abacavir susceptibility with a median fold decrease of 1.3 (range 0.5 – 11) compared to 29% (5/17) of the failure isolates in the twice daily arm with a median fold decrease of 0.92 (range 0.7 – 13).

MO Comment: *The NRTI-associated mutation, M184V/I, was the most commonly encountered resistance mutation in subjects who failed on either arm. The majority of subjects (>60%) who failed with M184V/I remained fully susceptible to ABC. The other 30+% of subjects had a greater than 2.5 fold shift in ABC susceptability. Other common treatment emergent resistance*

mutations were NRTI-associated mutation, L74V and NNRTI-associated, K103N.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

ABC's absolute bioavailability is ABC is rapidly absorbed with time to peak concentration occurring around 1 to 2 hours. Steady-state peak concentrations following the recommended dose of 300 mg BID is approximately

The apparent volume of distribution after intravenous administration is approximately /kg. Binding to plasma proteins is moderate (~ 49%). ABC is extensively metabolized with less than 2% excreted as the unchanged drug in the urine. ABC is primarily metabolized via two pathways, UDP-glucuronyl transferase and alcohol dehydrogenase pathways resulting in the glucuronide metabolite (361W94, ~ 36% of dose) and the carboxylate metabolite (2269W93, ~ 30% of dose). The remaining 15% of ABC equivalents found in the urine are minor metabolites each less than 2% of the total amount. The terminal systemic half-life of abacavir is approximately 1.5 hours.

Carbovir-triphosphate (CBV -TP) is considered the active, intracellular moiety of ABC, for inhibition of HIV reverse transcriptase; it has an intracellular half-life of 3.3 hours in CEM cells. Additionally, CBV-TP (1144U88-TP) levels produced from ABC increase linearly with increasing concentrations of ABC (from 0.1 to 100 μM), indicating that the formation of CBV-TP from ABC is not saturated over a wide (1000-fold) concentration range.

Study 10905 looking at CBV-TP levels over 24 hours after a single 300mg dose in subjects on a stable regimen of ABC 300mg BID was submitted in support of this sNDA. Please see Dr. Zheng's review for details. The following conclusion statements are taken from Dr. Belen's clinical review of study 10905:

1. After administration of a 300mg dose of abacavir, CBV-TP maintained levels with a long terminal half life in subject who had steady state levels based on a regimen of ABC 300 mg BID. Clinical data is still needed to determine the effectiveness of a 600mg once daily dosing regimen
2. The prolonged intracellular CBV-TP terminal half life of 20.64 hours supports the clinical evaluation of ABC as a once daily regimen for treatment of HIV infected patients.

MO Comment: *Dr. Zheng recently reviewed a population PK (not part of this sNDA submission) study which revealed that co-administration of ABC + d4T decreased ABC clearance by ~38%. This decrease in clearance could lead to an ~61% increase in ABC AUC. (Please see Dr. Zheng's review for further details). This finding will require further exploration in the form of a Phase IV commitment.*

B. Pharmacodynamics

No new data were submitted.

IV. Description of Clinical Data and Sources

A. Overall Data

The data source for this review comes from the October 3, 2004 GSK submission. The submission includes data collected from one large pivotal clinical trial (Study CNA30021) and one supportive PD study (CNA10905).

B. Tables Listing the Clinical Trials

Table # 2 Clinical Trials

Protocol Number (# and location of centers)	Study Design[1]	Treatments[2,3]	Form[4]	Total Number of Subjects Enrolled in Study[5]	Number of Subjects Receiving Standard ABC dose and regimen[6]	Duration of Exposure to ABC therapy	Age range (median) % Male/ Female (%Black/White /Other)
Clinical Pharmacology Studies: Pharmacokinetic and Population Pharmacokinetic Studies							
CNA30021 (120 international sites)	DB, Rand, MC	600mg ABC OAD vs. 300mg ABC BID + 3TC + EFV	ABC 300 mg Sulf tab + 3TC 150mg tab	784	384	48-84 weeks	18-71 (36) 81/19 27/54/19
Controlled Clinical Studies: Completed							
CNA10905 (2 US sites)	OL, SAR, PK	300mg ABC BID	ABC 300 mg Sulf tab or TZV	20	0	0	29-55 (40.5) 60/40 20/70/10

1 ADC: AIDS dementia complex, DB: Double-blind, CO: Crossover; MC: Multicenter, OL: Open-label, Par: Parallel, PC: Placebo-controlled, PK: Pharmacokinetic assessments, Rand:Randomized, SA: Single Arm, SD: Single-dose, Str: Stratified
2 3TC: lamivudine, 908: GW433908, 908/r: GW433908 plus ritonavir, ABC: abacavir, ART: antiretroviral therapy, COM: COMBIVIR, lamivudine 150mg and zidovudine 300mg, EFV:efavirenz, FDC: Fixed Dose Combination, IDV: indinavir, IDV/r: indinavir plus ritionavir, NFV: nelfinavir, NNRTI: non-nucleoside reverse transcriptase inhibitor, NVP: nevirapine, pcbo:placebo, PI: protease inhibitors, r: ritonavir, TDF: tenofovir disoproxil fumarate, TZV: TRIZIVIR, abacavir 300mg, lamivudine 150mg and zidovudine 300mg, ZDV: zidovudine
3 Medications dosed at standard, approved doses unless otherwise noted.
4 Cap: caplets, Soln: oral solution, Succ: Succinate, Sulf: Sulfate, Tab: Tablets
5 ABC once daily dose is 600mg; 3TC once daily dose is 300mg.
6 Unless otherwise noted, indicates intended length of study.

C. Postmarketing Experience

Once daily ABC is not yet approved in this country or in any other country , therefore, there are no postmarketing data available. Please refer to the Clinical Review of sNDA 20-977/S-11 and 20-978/S-12 for a summary of the postmarketing experience with the currently approved dose form of ABC 300 mg BID.

D. Literature Review

The applicant included selected articles relating to current expert opinion on treatment of HIV-1 infection, clinical trials using ABC, HSR epidemiology and risk assessment, viral resistance patterns and their impact on treatment with ABC and pharmacokinetics and pharmacodynamics of ABC.

V. Clinical Review Methods

A. How the Review was Conducted

Study CNA30021 was reviewed in detail for safety and efficacy. The applicant's safety and efficacy conclusions were confirmed by independent FDA analysis of the data. Dr. Fraser Smith, the Mathematical Statistics Reviewer, performed the statistical analyses confirming the primary efficacy endpoint, secondary endpoints and subgroup analyses. The Medical Officer reviewed study design, subject demographics, the primary and select secondary efficacy endpoints, clinical adverse events, and laboratory safety monitoring data, utilizing the JMP Statistical Discovery software. Data reviewed by the Medical Officer is contained in Module 5 of the sNDA.

The applicant and FDA analyses had minor differences in virologic response rates and virologic failure rates due to a few subjects who were reclassified based on the TLOVR algorithm. These minor differences had no impact on the conclusions reached.

Study CNA10905 was reviewed by Dr. Belen (Medical Officer) in detail with a focus on safety. These results are incorporated into the conclusions of the of the Integrated Summary of Safety and a detailed review can be found in Appendix B.

B. Overview of Materials Consulted in Review

The primary materials consulted included the entire sNDA, Clinical and Statistical reviews associated with the ABC accelerated and traditional approvals and correspondence from the applicant in response to requests for additional information to the NDA.

This sNDA was submitted to the FDA Electronic Document Room (EDR) as an electronic document consistent with the style of the Common Technical Document (CTD). The responses to requests for additional information were submitted in hard copy and in electronic form as appropriate.

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

DAVDP consulted DSI to inspect a random selection of investigators and sites that participated in CNA30021. Four investigators were selected for audit, Dr. Michael L. Sands, Dr. Nicholaos C. Bellos, Dr. Winkler G. Weinberg, and Dr. Joseph P. Lang. DSI found minor protocol violations and drug accountability violations at the site of Dr.Sands and minor source data versus data listing discrepancies and subjects failing to adhere to protocol directives at the site of Dr. Weinberg. Drs Bellos and Lang were found to be in compliance with Good Clinical Practices (GCP). Overall, DSI found no major deficiences that indicated compromise of the integrity of the data.

In addition, during the conduct and reporting of CNA30021, the GSK Clinical Compliance Department or a representative of the department performed eight independent, global investigator audits at five US, one Poland, one UK and one Spain site(s). GSK did not report any clinical trial misconduct.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

As per GSK the studies were conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, the Declaration of Helsinki, June 1964, as modified by the 48th World Medical Association, Republic of
South Africa, October 1996.

As per GSK the study protocols, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board.

E. Evaluation of Financial Disclosure

GSK, 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"), provided financial interest information for clinical investigators participating in studies covered by the rule included in this sNDA, namely CNA30021. Study CNA10905 is not a covered study, and therefore no Financial Disclosure information was provided for the investigators involved in this study.

As per the applicant, neither GSK nor its predecessor organizations compensates clinical investigators in such a way as the total amount could vary with the outcome of the study. Consequently, there are no disclosures in this category.

Based on available financial data, the $25,000 threshold for payments of other sorts was exceeded in the case of one investigator in study CNA30021 as follows:

Dr. Bisher Akil (investigator 5459) at center 29542 enrolled 3 patients (<1 %) of 782 patients enrolled in CNA30021. The primary efficacy analysis was performed post-hoc on the ITT population excluding these subjects from this center (29542), to assess the overall impact of this center's data on the outcome of the study. Results of this additional analysis to exclude patients from Dr. Akil's center indicated that there were no differences in measures or conclusions of the study.

GSK relied on information available internally to confirm that no clinical investigator participating in the covered clinical study CNA30021 had a proprietary interest in the tested product.

GSK relied upon equity information provided by the investigators through questionnaires to determine if the $50,000 threshold was exceeded in the case of any individual clinical investigator. If, according to their written commitment to GSK, investigators filed reports of updated equity interest information to account for any material changes in the 1-year period following study completion, these additional reports were relied on as well.

MO Comment: *Dr. Smith performed the primary efficacy analysis excluding the subjects enrolled by the three investigators with GSK financial holdings of more than $25,000. The outcome was not different than when the subjects were included.*

The original copy of Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators), Form FDA 3455 (Disclosure Financial Interests and Arrangements of Clinical Investigators)] and supporting tables, can be found in Module 1.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Results of study CNA30021 provide evidence of once daily ABC's durable antiviral effect when used in combination with other antiretroviral drugs in the treatment of HIV-1 infected, ARV naïve subjects.

The analysis of the primary efficacy endpoint for study CNA30021, time to loss of virologic response (TLOVR), was performed in accordance with methods proposed by the DAVDP Statistics team. Consequently after minor revisions to the proposed label, there was agreement between the DAVDP Review Team and the applicant on the presentation of efficacy results in the product label.

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

The efficacy database results solely from pivotal study CNA30021. Supportive study CNA10905 is a PK study, which did not contribute any information to the efficacy of the investigational product.

D. Detailed Review of Trials by Indication

1.0 Study CNA30021 – A Phase III, 48-week, Randomized, Double-blind, Multicenter Study to Evaluate the Safety and Efficacy of ABC (ABC) 600mg Once daily (OAD) vs ABC 300mg BID in Combination with Lamivudine (3TC) (300mg once daily)and Efavirenz (EFV) (600mg once daily) in Antiretroviral Therapy Naïve HIV-1 Infected Subjects

1.1 Study Design

Study CNA30021 was a Phase III, 1:1 randomized, double-blind, multicenter, international study ofART-naïve HIV-1 infected subjects designed to evaluate the antiviral effects (as measured by plasma HIV-1 RNA) and safety of once daily dosing of ABC (600mg once daily (OAD)) versus the recommended twice daily dosing of ABC (300mg twice daily (BID)), as a component of triple-drug therapy including 3TC (300mg once daily) and EFV (600mg once daily). Enrollment was stratified at screening by plasma HIV-1 RNA to one of two strata (100,000 and >100,000 copies/mL).

MO Comment: *Of note, CNA30021 was designed as a non-inferiority trial with a pre-specified delta margin of 12%. A non-inferiority margin of 12% may be a bit generous given that the two treatment arms only differ in the dosing frequency of one ARV and therefore the antiviral activity of the regimens are expected to perform similarly.*

Subjects were stratified prior to randomization based on screening HIV RNA viral load (less than or greater than 100,000 copies/mL). Subjects were then centrally randomized 1:1 to one of two treatment arms:

Arm 1: ABC 600mg OAD + ABC placebo (BID) + 3TC 300mg once daily + EFV 600mg once daily

Arm 2 : ABC 300 mg BID + ABC placebo (OAD) + 3TC 300 mg once daily + EFV 600mg once daily

Subjects who permanently discontinued randomized study drug (ABC OAD or ABC BID) could remain on study, but were considered treatment failures at the time of switch. Subjects could change their background study drugs (3TC or EFV) to another licensed antiretroviral without being considered treatment failures.

Subjects were asked to return to the clinic at Day 1, Weeks 2, 4, 8, 12, and every 12 weeks thereafter until the last subject enrolled reached 48 weeks of treatment. Randomized subjects were eligible to receive study drugs until the last subject enrolled reached 48 weeks of treatment. All subjects were scheduled for a 4-week post treatment follow up visit (Follow-up). Monitoring for clinical disease progression, adverse events, drug toxicity via hematology, chemistry and liver function testing, pregnancy testing and immunologic and virologic assessments of efficacy were performed at each visit. The Roche Amplicor Standard 1.0 PCR was used at the first assessment, however, HIV-1 RNA values reported below 50,000 copies/mL were re-assayed using Roche Amplicor UltraSensitive 1.0 PCR (any HIV-1 RNA measurements which exceeded the analysis range of the UltraSensitive PCR Assay were re-assayed and reported using the Standard PCR Assay). Each subsequent visit after Screening utilized the same assay as the previous assessment.

Adverse events (AEs)and laboratory abnormalities were graded by the modified Division of AIDS (DAIDS) toxicity scales. All subjects with a suspected HSR were reported as a Serious Adverse Event (SAE) and ABC was permanently discontinued if an HSR could not be ruled out. Subjects were also permanently discontinued from study for a recurrent Grade 3 AE that recurred within 28 days of the initial Grade 3 AE and all Grade 4 AEs. There were no criteria for study drug discontinuation due to lack or loss of virologic response.

1.2 Applicant's Analysis Plan

The primary objective of study CNA30021 was to compare the efficacy of ABC OAD to ABC BID determining the proportion of subjects with plasma HIV-1 RNA $\leq$50 copies/mL through 48 weeks and adjusted by randomization strata. Secondary objectives were to compare the as-treated antiviral effects of the two therapies based on the proportion of subjects with plasma HIV-1 RNA $\leq$50 copies/mL, to compare cumulative antiviral effects of the two therapies and to compare the safety and tolerability of the two therapies. Statistical analyses were conducted after the last subject completed the 48 week treatment phase. No interim analyses were planned or conducted. No data monitoring committees were utilized.

The following three subject populations were used in the analyses:

- Intent-to-treat (ITT) Exposed Population included all subjects randomized and exposed to at least one dose of any study medication. This was the primary population for all efficacy analyses.
- Safety Population included all subjects exposed to at least one dose of study medication; however, assignment to an analysis population was based on medication received not on randomized assignment.
- As-treated Population included all subjects with study data available while still taking their randomized treatment regimen.

The number and percentage of subjects randomized, subjects randomized but not treated, subjects withdrawn from randomized treatment and reason for withdrawal, and subjects' deaths were summarized for each treatment group. Protocol violations were summarized. If major protocol violations were numerous (>5% of subjects), GSK planned to prepare summary tables of key virologic and immunologic responses to analyze the impact of major protocol violators on the two treatment groups.

The primary efficacy measure was comparison of the proportion of subjects with plasma HIV-1 RNA levels ≤50 copies /mL at Week 48 and adjusted by the randomization strata. The analysis was based on Intent-to-Treat (ITT) Exposed Population, which included subjects exposed to at least one dose of study medication. A responder was defined as a subject who achieved a confirmed plasma HIV-1 RNA ≤50 copies/mL and had not yet lost the virologic response by Week 48, as defined by the time to loss of virologic response algorithm (TLOVR).

Secondary efficacy endpoints included the following:

1. Comparison of safety by the number of subjects who discontinued therapy.

2. Comparison of on-treatment observed (namely, the As Treated population) antiviral efficacy based on the proportion of subjects with plasma HIV-1 RNA levels ≤50 copies/mL at Week 48.

3. Time to loss of virologic response. For analysis, the following algorithm was used:
   a) For subjects who never achieved a confirmed plasma HIV-1 RNA level ≤50 copies/mL (i.e., two consecutive visits ≤50 copies/mL) before the following events, these subjects were considered a failure at time 0:
      • Death
      • Permanent discontinuation of randomized study drugs (ABC or ZDV)
      • Introduction of a new ART, except changes to background drugs (3TC or EFV)
      • Last visit.
   b) For subjects who achieved a confirmed plasma HIV-1 RNA ≤50 copies/mL; the TLOVR was the earliest time of:
      • Death

- Introduction of a new ART, except changes to background drugs (3TC or EFV)
- Confirmed plasma HIV-1 RNA above 50 copies/mL (i.e., two consecutive visits above 50 copies/mL or one visit above 50 copies/mL followed by discontinuation).

For subjects who did not meet the definitions in a) or b) and were suppressed at the time of the last visit, the record was censored at the time of the last study visit.

4. Cumulative antiviral efficacy, measured as the integrated decresase in plasma HIV-1 RNA, defined as the average area under the plasma HIV-1 RNA curve minus baseline (AAUCMB).

5. Immunologic efficacy, measured as absolute change from baseline CD4+ cell count at 48 weeks and integrated increase in CD4+ cell count, defined AAUCMB.

6. Clinical disease progression rates as measured by the number of subjects who progressed to new events.

7. Assessment of rash/hypersensitivity reaction by detailed clinical and laboratory investigations.

8. Comparison of the development of resistance between the two treatment groups.

The analysis of secondary endpoints included ITT-exposed and As-Treated populations.

All available safety data (including data beyond 48 weeks) were included in the analysis of safety data. The safety population was used for the safety analyses. Drug exposure characterized by days on treatment and total days on full dose of study drug was presented by treatment group. Each adverse event was classified by body system and coded group term using MedDRA terminology and the HIV-specific grouping of MedDRA terms. Adverse events were tabulated by treatment group, maximum intensity, seriousness, and attributability to study drug. For each graded laboratory parameter, treatment-emergent toxicity grades were presented by treatment group.

1.3.1 Study Population and Subject Disposition

A total of 730 adult subjects (365 per treatment group) with HIV-1 infection were planned for enrollment into this study. Subjects eligible for study enrollment were HIV- 1 infected, ART naïve (defined as less than 7 days of any prior approved or experimental ART or having 14 days or less of AZT monotherapy), males or females > 18 years of age, with an HIV-1 RNA level > 400 copies/mL and a CD4+ cell count > 50 cells/mm3 who were willing and able to sign an Informed Consent Document. Eligible females had to be either of non-childbearing potential or if of childbearing potential they had to have a negative pregnancy test at screening

and agree to one of the following birth control methods: abstinence, sterilization, double barrier method contraception, or IUD.

Subjects were not eligible for enrollment if they were unlikely to be able to complete the 48 weeks of treatment, currently abused alcohol or illicit drugs, had malabsorption or gastrointestinal dysfunction that might interfere with the absorption of oral medications, had clinically relevant hepatitis or pancreatitis in the last 6 months, had unacceptable laboratory evaluations that indicated hematologic, hepatic, pancreatic or renal compromise, were pregnant or breast feeding, participated in an investigational HIV vaccine trial and received a dose of vaccine within the 3 months prior or had gene therapy, had serious underlying medical conditions that would compromise the safety of the subject, had an active AIDS diagnosis, or were receiving other investigational treatments.

Subjects could be terminated prior to completing study for any of the following reasons:

- subject or investigator non-adherence with protocol procedures or subject non-adherence to therapy
- at the request of the subject, investigator or sponsor
- progression of any medical condition, which would preclude further study participation
- if the subject required another investigational drug that would jeopardize the validity of the study results
- female subjects who became pregnant
- female subjects who did not use effective barrier methods of contraception
- subjects who required cytotoxic chemotherapy or radiation therapy (with the exception of local treatment for KS).

A total of 784 adult subjects were randomized (392 to each of the two study arms). The first subject was enrolled on June 13, 2001 and the last subject completed the Week 48 visit on March 26, 2003. Fourteen (14) subjects were enrolled and randomized, but never received study drug (eight on the ABC OAD arm and six on the ABC BID arm). Of the remaining 770 subjects, 384 received at least one dose of ABC OAD + 3TC + EFV and 386 received at least one dose of ABC BID + 3TC + EFV.

The demographic and baseline characteristics were similar for both treatment groups with the exception of gender where the ABC BID group had a greater percentage of female subjects (21%) than the ABC OAD group (16%) and baseline CD4 count where the ABC OAD had a greater percentage of subjects (34% vs 29%) with baseline CD4 counts below 200 (Tables 3 and 3). Subjects were predominately male (81%), white (54%), median age of 36 years (range 18-71) with a median HIV-RNA of 4.89 log10 copies/mL and median CD4 cell count of 262 cells/mm3.

Table # 3 Demographic Characteristics (ITT-Exposed Population - CNA30021)

Demographic Characteristic	ABC OAD N=384	ABC BID N=386	Total N=770
Gender - n (%)			
Male	323 (84%)	304 (79%)	627 (81%)
Female	61 (16%)	82 (21%)	143 (19%)
Age (years)			
Median	36	36	36
Range	18-71	18-71	18-71
Race - n (%)			
White	207 (54%)	207 (54%)	414 (54%)
Black	99 (26%)	111 (29%)	210 (27%)
American Hispanic	60 (16%)	55 (14%)	115 (15%)
Asian	10 (3%)	8 (2%)	18 (2%)
Other	8 (2%)	5 (1%)	13 (2%)
Weight (kg)			
Median	72.2	72.4	72.3
Range	44.7-150.0	38.4-170.5	38.4-170.5
Randomization Strata - n (%)			
HIV-1 RNA ≤100,000 copies/mL	217 (57%)	217 (56%)	434 (56%)
HIV-1 RNA >100,000 copies/mL	167 (43%)	169 (44%)	336 (44%)
Baseline CD4+ Count - n (%)			
<200 cells/mm^3	130 (34%)	109 (29%)	239 (31%)
200 -350 cells/mm^3	144 (38%)	171 (44%)	315 (41%)
>350 cells/mm^3	109 (28%)	105 (27%)	214 (28%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 58, Table 4

MO Comment: *Subgroup analyses by gender of the different efficacy parameters and safety parameters did not reveal any gender trends or differences. Therefore, the gender disparity between the two arms does not appear to have any clinical relevance.*

The baseline CD4 disparity may have placed the ABC OAD at risk for more HIV associated events and adverse events in general. This risk is not likely offset by the fact that the median baseline CD4 value for the ABC OAD group was slightly higher than the ABC BID group indicating that overall the ABC OAD had subjects whose CD4 counts were on average higher than those of the subjects in the ABC BID group.

Table 4 Baseline Characteristics (ITT-Exposed Population - CNA30021)

Baseline Characteristic	ABC OAD N=384	ABC BID N=386	Total N=770
Baseline Values - median (range)			
HIV-1 RNA PCR (copies/mL)	81,684 (1,127-9,872,576)	74,894 (399-3,893,696)	78,521 (399-9,872,576)
HIV-1 RNA PCR (log_{10} copies/mL)	4.91 (3.05-6.99)	4.87 (2.60-6.59)	4.89 (2.60-6.99)
CD4+ count (cells/mm^3)	264 (21-918)	259 (37-886)	262 (21-918)
CD8+ count (cells/mm^3)	787 (140-4741)	771 (95-2568)	779 (95-4741)
Confirmed Hepatitis - n (%)			
Hepatitis B surface antigen	18 (5%)	16 (4%)	34 (4%)
Hepatitis C antibody	55 (14%)	47 (12%)	102 (13%)
Hepatitis B & C co-infected	2 (<1%)	1 (<1%)	3 (<1%)
CDC Classification of HIV - n (%)			
Class A - asymptomatic	298 (78%)	285 (74%)	583 (76%)
Class B – symptomatic, not AIDS	63 (16%)	70 (18%)	133 (17%)
Class C – AIDS	23 (6%)	30 (8%)	53 (7%)
Missing	0	1 (<1%)	1 (<1%)
Other non-CDC HIV-1 Associated Condition - n (%)			
Yes	9 (2%)	21 (5%)	30 (4%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 59, Table 5

Table 5 summarizes the outcomes of all randomized subjects at the end of the study record as per GSK. As per GSK 76% subjects on each study arm completed at least 48 weeks on study (defined as 295 days of study treatment). The remainder of subjects discontinued for a variety of reasons the most frequent in both arms being lost to follow-up.

Table 5 Subject Disposition (All Randomized Subjects - CNA30021) per GSK's Analysis

	ABC OAD n (%)	ABC BID n (%)	Total n (%)
Total Randomized (N)	392 (100%)	392 (100%)	784 (100%)
Not treated	8 (2%)	6 (2%)	14 (2%)
Treated	**384**	**386**	**770**
Completed	290 (76%)	294 (76%)	584 (76%)
Discontinued	94 (24%)	92 (24%)	186 (24%)
<48 weeks of treatment	58 (15%)	63 (16%)	121 (16%)
≥48 weeks of treatment[1]	36 (9%)	29 (8%)	65 (8%)
Reason for Discontinuation			
Number discontinued	94	92	186
Adverse event	22 (23%)	25 (27%)	47 (25%)
Consent withdrawn	12 (13%)	9 (10%)	21 (11%)
Lost to follow-up	32 (34%)	35 (38%)	67 (36%)
Clinical progression	1 (1%)	1 (1%)	2 (1%)
Protocol violation	4 (4%)	2 (2%)	6 (3%)
Insufficient viral load response	6 (6%)	5 (5%)	11 (6%)
Other	17 (18%)	15 (16%)	32 (17%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 54, Table 1
1. Subjects who discontinued after 48 weeks of treatment may have been counted as responders at the 48-week analysis.

MO Comment: *The applicant's use of the End of Study Record to determine subject disposition and reasons for discontinuation is potentially misleading. Firstly, the end of study record captures subjects who remained on study, and who withdrew from the study and why. The end of study record does not capture who remained on randomized treatment and who withdrew from randomized treatment and why. It is this reviewer's opinion that the most clinically relevant information is the number of subjects who remained on randomized treatment. Secondly, the end of study record captures what occurs at the 4-week post treatment visit. For example if a subject at Week 30 discontinues randomized treatment because of an adverse event and fails to return for the 4-week post-treatment visit then that subject is considered a "lost to follow-up" not an "adverse event" as the reason for discontinuation in the End of Study Record. Although a "lost to follow-up" is technically what occurred at the End of the Study, the "adverse event" is the event that drove the discontinuation.*

Table 6 summarizes this reviewer's analysis of Subject Disposition using the end of randomized treatment record to determine the numbers and proportion of subjects who completed treatment, discontinued treatment and the reasons for discontinuation. The two arms were comparable in all respects except the OAD arm had more discontinuations due to AEs while the BID arm had more discontinuations due to lost to follow-up.

Table 6 Subject Disposition (All Randomized Subjects - CNA30021) per FDA's Analysis

	ABC OAD n (%)	ABC BID n (%)	Total n (%)
Total Randomized (N)	392 (100%)	392 (100%)	784 (100%)
Not treated	8 (2%)	6 (2%)	14 (2%)
Treated	**384**	**386**	**770**
Completed randomized investigational treatment	275 (71%)	281 (73%)	556 (72%)
Discontinued randomized investigational treatment	109 (28%)	105 (27%)	214 (28%)
<48 weeks of treatment	98 (26%)	94 (24%)	192 (25%)
≥48 weeks of treatment[1]	11 (3%)	11 (3%)	22 (3%)
Reason for Discontinuation			
Number discontinued	109	105	214
Adverse event	53 (49%)	45 (43%)	98 (46%)
Consent withdrawn	11 (10%)	10(10%)	21 (10%)
Lost to follow-up	26 (24%)	30 (29%)	56 (26%)
Clinical progression	1 (<1%)	1 (1%)	2 (<1%)
Protocol violation	2 (2%)	2(2%)	4 (2%)
Insufficient viral load response	4 (4%)	3 (3%)	7 (3%)
Other	12 (11%)	14 (13%)	26 (12%)

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 135, Table 12.7
1. Subjects who discontinued after 48 weeks of treatment may have been counted as responders at the 48-week analysis.

***MO Comment**: The FDA analysis found that fewer subjects completed 48 weeks of "randomized treatment" (72% total) and that the most common reason for discontinuation of "randomized treatment" was adverse events (46% total compared to GSK's 25% total), whereas in GSK's analysis there were more subjects who completed 48 weeks of "study"(76% total) and the most common reason for discontinuation was lost to follow-up (36% total compared to FDA's 26% total).*

The important similarity between the FDA and GSK's analyses is that the completion and discontinuation rates did not significantly differ between the two arms.

*Overall, this reviewer believes that the most clinically relevant subject disposition data reveals that nearly three-quarters of subjects completed the study on their randomized treatment and that the majority of subjects who did not stay on their randomized treatment discontinued because of adverse events. Of note, virologic failure did not mandate treatment or study discontinuation, and as presented above, there were only seven subjects captured as discontinuing **randomized treatment** due to an insufficient viral load and eleven subjects captured as discontinuing **study** due to an insufficient viral load.*

1.4 Efficacy Results

Please refer to Dr. Smith's Statistical Review for a comprehensive analysis of the efficacy results.

The primary efficacy endpoint was comparison of the proportion of subjects in the ITT-Exposed Population with plasma HIV-1 RNA levels < 50 copies/mL at Week 48 based on the TLOVR algorithm. The results of GSK and FDA's analyses of the primary endpoint according to baseline viral load stratification are shown in Tables 7 and 8, respectively.

Table 7 Statistical Evaluation of Non-inferiority of Virologic Response at Week 48 Based on Plasma HIV-1 RNA <50 copies/mL using the TLOVR algorithm (ITT-Exposed Population - CNA30021) per GSK's Analysis

Strata	ABC OAD N=384 n (%)	ABC BID N=386 n (%)	Point Estimate (%)	95% Confidence Interval
Stratified				
≤100,000 copies/mL	141/217 (65%)	145/217 (67%)	-1.8	-10.8, 7.1
>100,000 copies/mL	112/167 (67%)	116/169 (69%)	-1.6	-11.6, 8.4
Unstratified			-1.7	-8.4, 4.9
Total	253/384 (66%)	261/386 (68%)		

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 62, Table 7

As per GSK's analysis the two treatment arms did not differ significantly in their virologic response rates at Week 48 for both the stratified and unstratified groups, and the 95% confidence intervals fell within the non-inferiority boundary of 12%.

MO Comment: *It appears that a standard non-inferiority margin of 12% was set in the original protocol without a specific rationale being applied to this particular study. Given that the two treatment arms only differ in the dosing frequency of one ARV the antiviral activity of the regimens are expected to perform almost identically given clinical trial constraints. In the end however, the points estimates in this study were comparable.*

Fifteen additional patients (51012, 51124, 51643, 51913, 52473, 52701, 52761, 52821, 53753, 53758, 51132, 51431, 51550, 52443 and 52445), 6 in the ABC OAD treatment group and 9 in the ABC BID treatment group were reclassified as virologic failures because their HIV-1 RNA rebounded (exceeded 50 copies/mL) at their last Week 48 visit after being suppressed at 2 prior consecutive visits.

MO Comment: *This reclassification was performed to be consistent in the application of the TLOVR algorithm. Examination of each of the subject's viral decay curve would not necessarily be considered a "failure" from a clinical perspective (please see further MO comments below).*

These results are similar to the GSK's except there is a 1-2% decrease in the percentage of responders in both treatment groups.

Table 8 Statistical Evaluation of Non-inferiority of Virologic Response at Week 48 Based on Plasma HIV-1 RNA <50 copies/mL using the TLOVR algorithm (ITT-Exposed Population - CNA30021) per FDA's Analysis

Strata	ABC OAD N=384 n (%)	ABC BID N=386 n (%)	Point Estimate (%)	95% Confidence Interval
Stratified				
≤100,000 copies/mL	139/217 (64%)	140/217 (65%)	-0.5	-9.5, 8.6
>100,000 copies/mL	108/167 (65%)	112/169 (66%)	-1.6	-11.8, 8.6
Unstratified			-1.0	-7.7, 5.8
Total	247/384 (64%)	252/386 (65%)		

MO Comment: *The reclassification of the 15 subjects as virologic failures had little impact on the comparison between the treatment groups. The FDA's analysis results will be used in the label.*

Tables 9 and 10 present the proportion of subjects who were virologic responders at each study visit through Week 48 as per GSK's and FDA's analyses. The tables differ only in the number and proportion of subjects who were virologic responders at Week 48 in both arms due to the 15 subjects who were reclassified as failures at Week 48.

Table 9 Proportion of Subjects with Virologic Response Based on Plasma HIV-1 RNA <50 copies/mL through Week 48 (ITT-Exposed Population - CNA30021) per GSK's analysis

Study Week	ABC OAD N=384 n (%) Responder	ABC BID N=386 n (%) Responder
Week 2	16 (4%)	16 (4%)
Week 4	35 (9%)	44 (11%)
Week 8	84 (22%)	106 (27%)
Week 12	156 (41%)	170 (44%)
Week 24	246 (64%)	259 (67%)
Week 36	256 (67%)	264 (68%)
Week 48	253 (66%)	261 (68%)

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 66, Table 9

The proportion of virologic responders appeared slightly higher for ABC BID subjects, particularly at Week 8. However the difference between the two treatment groups at Week 8 was not statistically significant (p=0.079).

Table 10 Proportion of Subjects with Virologic Response Based on Plasma HIV-1 RNA <50 copies/mL through Week 48 (ITT-Exposed Population - CNA30021) per FDA's analysis

Study Week	ABC OAD N=384 n (%) Responder	ABC BID N=386 n (%) Responder
Week 2	16 (4%)	16 (4%)
Week 4	35 (9%)	44 (11%)
Week 8	84 (22%)	106 (27%)
Week 12	156 (41%)	170 (44%)
Week 24	246 (64%)	259 (67%)
Week 36	256 (67%)	264 (68%)
Week 48	247 (64%)	252 (65%)

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 66, Table 9

MO Comment: *Although the response rates were comparable between arms in both GSK's and the FDA's analyses, the number of virologic failures at Week 48 was initially concerning. However, evaluation of the individual case details revealed that a number of these subject reclassifications may have been due more to the application of the TLOVR algorithm than to a true clinical failure: 4 subjects virologically failed with VL < 100, 2 subjects virologically failed with VL < 200, 8 subjects had unconfirmed rises in VL, and 4 subjects were considered failures due to a second 48 week visit VL where they undetectable at the first 48 week visit. Unfortunately the TLOVR algorithm is not designed to take this type of information into account.*

The outcomes at Week 48 for the ITT-Exposed Population are summarized in Table 11.

Table 11 Summary of Outcomes at Week 48 (based on TLOVR) for Plasma HIV-1 RNA <50 copies/mL (ITT-Exposed Population - CNA30021) per GSK's Analysis

Outcome	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Responder	253 (66%)	261 (68%)
Virologic Failure	38 (10%)	32 (8%)
Rebound	9 (2%)	8 (2%)
Never suppressed through Week 48	27 (7%)	21 (5%)
Insufficient viral load response[1]	2 (<1%)	3 (<1%)
Discontinued or changed therapy due to AE	50 (13%)	42 (11%)
Discontinued or changed therapy due to other reasons	43 (11%)	51 (13%)
Consent withdrawn	10 (3%)	10 (3%)
Lost to follow-up	20 (5%)	23 (6%)

Outcome	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Protocol violation	1 (<1%)	2 (<1%)
Insufficient CD4+ response	0	0
Clinical progression	1 (<1%)	1 (<1%)
Other	9 (2%)	14 (4%)
Change of ART[2]	2 (<1%)	1 (<1%)

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 67, Table 10.
1. As recorded on the treatment discontinuation CRF page
2. Excluding changes to background medications (3TC and EFV)

As per GSK's analysis, in the ABC once daily group, 66% (253/384) of subjects were defined as responders, as compared with 68% (261/386) of subjects in the ABC twice daily group. The number of subjects defined as virologic failures was slightly higher in the OAD group (10%) versus the BID group (8%). Twenty-seven (7%) subjects in the ABC once daily group were never suppressed at Week 48, as compared with the 21 (5%) subjects in the ABC twice daily group. As per a GSK analysis, twenty-four (89%) of these 27 subjects in the ABC once daily group and 19 (90%) of the 21 subjects in the ABC twice daily group who had not achieved confirmed suppression of plasma HIV-1 RNA <50 copies/mL by Week 48 did achieve confirmed suppression of plasma HIV-1 RNA <400 copies/mL by Week 48.

In addition the OAD arm had slightly more discontinuations due to adverse events while the BID arm had more discontinuations due to other reasons.

Table 12 presents the FDA's analysis of the summary of outcomes at Week 48 based on the TLOVR algorithm taking into account the 15 subjects who were reclassified as virologic failures due to VL rebound.

Table 12 Summary of Outcomes at Week 48 (based on TLOVR) for Plasma HIV-1 RNA <50 copies/mL (ITT-Exposed Population - CNA30021) per the FDA's analysis

Outcome	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Responder	247 (64%)	252 (65%)
Virologic Failure	44 (11%)	41 (11%)
Rebound	15 (4%)	17 (4%)
Never suppressed through Week 48	27 (7%)	21 (5%)
Insufficient viral load response[1]	2 (<1%)	3 (<1%)
Discontinued or changed therapy due to AE	50 (13%)	42 (11%)
Discontinued or changed therapy due to other reasons	43 (11%)	51 (13%)
Consent withdrawn	10 (3%)	10 (3%)
Lost to follow-up	20 (5%)	23 (6%)
Protocol violation	1 (<1%)	2 (<1%)

Outcome	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Insufficient CD4+ response	0	0
Clinical progression	1 (<1%)	1 (<1%)
Other	9 (2%)	14 (4%)
Change of ART[2]	2 (<1%)	1 (<1%)

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 67, Table 10.
1. As recorded on the treatment discontinuation CRF page
2. Excluding changes to background medications (3TC and EFV)

MO Comment: *Outcomes in Tables 11 and 12 are based on the TLOVR algorithm through Day 379, which is why the number of subjects who withdrew from randomized treatment do not match the numbers in Table 6 on Subject Disposition, which is based on the subject's entire study length.*

Although, the number of virologic failures is comparable between arms, there are significantly more virologic failures in this clinical trial (both GSK's and the FDA's analyses) compared to the 6% virologic failure rate observed in CNA30024 (the pivotal trial supporting ABC traditional approval, which used the same regimen of ABC + 3TC + EFV.) A sensitivity analysis by Dr. Smith showed a statistically significant difference between the virologic failures on the ABC OAD arm in CNA30021 (n=44, 11%) and the ABC BID arm in CNA30024 (n=21, 6%) with a p-value of 0.026. Neither comparison of the virologic failure rate on the OAD arm versus the BID arm in CNA30021, nor comparison of the virologic failure rates on the two BID arms (CNA30021 versus CNA30024)was statistically significant. Additionally, a similar sensitivity analysis using a cutoff of VL >200 copies/mL showed no statistically significant difference between the OAD arm and either of the BID arms.

MO Comment: *Although the difference between the incidence of virologic failures in the OAD arm (CNA30021) and the BID arm (CNA 30024) is statistically significant, it should be considered in the context of 1) it is a cross study comparison; 2) it was only significant when the 15 additional virologic failures were added based on a conservative interpretation of the TLOVR algorithm; and 3) the difference was not statistically significant when the VL cutoff was inreased to < 200 copies/mL.*

The observed absolute CD4+ counts and change from baseline CD4+ counts over 48 weeks for the ITT-Exposed Population are summarized in Table 13.

Table 13 Summary of CD4+ Cell Counts (cells/mm 3) and Change from Baseline (ITT-Exposed Population, Observed - CNA30021)

Study Week	n	ABC OAD N=384 Median (cells/mm³)	Change from Baseline	n	ABC BID N=386 Median (cells/mm³)	Change from Baseline
Baseline	383	264		385	259	
Week 2	353	329	60.0	346	327	68.5
Week 4	353	355	86.0	351	349	90.0
Week 8	348	375	114.5	343	379	112.0
Week 12	345	387	121.0	351	407	133.0
Week 24	330	431	157.0	339	428	163.0
Week 36	321	450	174.0	319	443	174.0
Week 48	309	468	188.0	309	471	200.0

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 72, Table 15

MO Comment: *The median CD4 count increase was robust and comparable on both arms.*

Table 14 presents the virologic response rates for the As Treated population.

Table 14 Statistical Evaluation of Non-inferiority based on the Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 (As-Treated Population - CNA30021)

Strata	ABC OAD N=266 n (%)	ABC BID N=265 n (%)	Point Estimate (%)	95% Confidence Interval
Stratified				
≤100,000 copies/mL	132/145 (91%)	126/145 (87%)	4.1	-3.1, 11.3
>100,000 copies/mL	99/121 (82%)	103/120 (86%)	-4.0	-13.3, 5.3
Unstratified			0.4	-5.4, 6.2
Total	231/266 (87%)	229/265 (86%)		

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 68, Tables 11 and 13.8

MO Comment: *Overall the ABC OAD and BID As Treated groups performed similarly. Although the As Treated population is not the ideal population to analyze in a clinical trial designed to test for superiority of a drug, in a non-inferiority trial it is important to consider the outcome of all populations. In this study the ABC OAD >100,000 strata did not meet the pre-defined delta margin of 12% non-inferiority based on the 95% confidence intervals. Of course caution must be exercised in drawing any conclusions from a sensitivity analysis of a population that the study was not designed or powered to analyze. However, similar results were seen for the As Treated population in CNA30024 (pivotal study supporting traditional approval of ABC) and it is noteworthy to add that for both studies viral load stratification occurred pre-randomization.*

Table 15 summarizes the incidence of clinical progression during the 48 Week study period by treatment arms.

Table 15 Summary of HIV Associated Conditions Progression of HIV Disease (ITT-Exposed Population - CNA30021)

Subject Number	Screening CDC Classification	Disease Progression CDC Classification	Clinical Event
ABC OAD			
51382	Class C	Death	Pneumonia, recurrent
51910	Class B	Class C	Lymphoma, immunoblastic
51911	Class A	Class C	Mycobacterium TB
51243	Class A	Death	Fatal AE (lymphoma, acute renal failure)
52384	Class A	Class C	Toxoplasmosis of brain
51010	Class A	Class C	Herpes simplex
ABC BID			
52879	Class A	Class C	Kaposi s sarcoma cutaneous
51529	Class B	Death	Fatal AE (sepsis, diabetes)
51671	Class B	Class C	Kaposi s sarcoma cutaneous
52289	Class B	Class C	Kaposi s sarcoma cutaneous
52701	Class A	Death	Fatal AE (undetermined cause)
52703	Class B	Death	Lymphoma, Burkitt s
52229	Class B	Class C	Lymphoma, immunoblastic
51014	Class C	New Class C	Kaposi s sarcoma cutaneous
52505	Class C	New Class C	Pneumocystis carinii pneumonia
52908	Class A	Class C	Pneumocystis carinii pneumonia

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 77, Table 18

Incidences of HIV-1 disease progression were low and comparable between treatment groups during the entire study. A total of 6 (2%) subjects in the ABC once daily group and 10 (3%) subjects in the ABC twice daily group reported a new CDC Class C event or death during the conduct of the study. Subject 51480 had no baseline CDC Class rating.

MO Comment: *Please see Fatal AE narratives for a summary of all deaths. No deaths were attributed to study drug.*

Although HIV-1 RNA of < 400 copies was neither a primary nor a secondary endpoint the results of this analysis for the ITT population is presented below (Table 16).

Table 16 Statistical Evaluation of Non-inferiority of Virologic Response at Week 48 Based on Plasma HIV-1 RNA <400 copies/mL using the TLOVR Algorithm (ITT-Exposed Population - CNA30021)

Strata	ABC OAD N=384 n/N (%)	ABC BID N=386 n/N (%)	Point Estimate (%)	95% Confidence Interval
Stratified			-0.4	-6.7, 5.9
≤100,000 copies/mL	151/217 (70%)	148/217 (68%)	1.4	-7.3,10.1
>100,000 copies/mL	125/167 (75%)	131/169 (78%)	-2.7	-11.8, 6.4
Unstratified			-0.4	-6.7, 5.9
Total	276/384 (72%)	279/386 (72%)		

Source: Clinical Study Report CNA 30021, module 5.3.5.1, p. 77, Table 19

The 95% confidence intervals support the non-inferiority of ABC OAD compared with ABC BID.

E. Efficacy Conclusions

For study CNA30021 all of the efficacy analyses conducted by the applicant and confirmed by the FDA clinical/statistical review team concluded that overall ABC OAD was non-inferior to ABC BID when given in combination with 3TC and EFV over a 48 week study period in treatment-naïve subjects. The two groups had a similar number of virologic responder, treatment and study discontinuations, and virologic failures. While the ABC OAD group had slightly more discontinuations due to adverse events, the ABC BID group had slightly more discontinuations due to "other events". Additionally, the incidence of HIV-related disease progression was similar between the ABC OAD and ABC BID groups.

No statistically significant difference was seen between the unstratified groups for the primary endpoint of VL < 50 copies/mL in the ITT or As Treated group. However, in the As Treated population subgroup analysis the > 100,000 strata in the OAD group did not meet the predetermined non-inferiority delta margin of 12%. Given the smaller sample size and the fact that this is a subgroup analysis, it is difficult to draw any conclusions from these results. However, ABC's ability to provide durable antiviral activity in subjects with baseline viral loads of >100,000 has been a recurrent concern that as of yet well-controlled, clinical trials have not been able to answer. This disparity between the OAD and BID > 100,000 strata highlights this issue once again.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Based on the 48-week data submitted in CNA30021, ABC OAD, in combination with other antiretrovirals, has a safety profile that is acceptable and in general similar to that of ABC BID. The incidences of AEs, treatment-emergent AEs, and severe or serious AEs were similar

between the ABC OAD + 3TC + EFV and ABC BID + 3TC + EFV treatment groups with the following exception: the OAD arm had significantly more severe ABC hypersensitivity reaction (HSR) and diarrhea AEs. Additionally hypotension was seen in 11% of the subjects who experienced ABC HSR on the OAD arm compared to 0 subjects on the ABC BID arm, which was clinically significant, but not statistically significant. In general, the safety results demonstrated that both regimens were well tolerated, and safety profiles were comparable over 48 weeks of randomized treatment exposure.

HSR is the most serious of the listed and expected adverse events associated with ABC. In CNA30021, HSR was reported at a slightly higher rate (9% in the OAD arm, 7% in the BID arm) than the labeled rate of 5%. This rate is consistent with rates of 8% observed in each of the two pivotal studies supporting traditional approval of ABC. There were no fatalities attributable to either treatment regimen.

There is no evidence indicating ABC OAD contributed to any adverse clinical manifestations that have not been previously described for ABC BID.

B. Description of Patient Exposure

Study drug exposure is presented in Table 17 below.

Table 17 Extent of ABC Exposure (Safety Population - CNA30021)

	ABC OAD N=384	ABC BID N=386
Total Days on Treatment		
Median	372.0	366.5
Range	1.0-585.0	1.0-581.0
Length of Exposure - n (%)	384	386
≤8 weeks	57 (15%)	49 (13%)
>8 to ≤16 weeks	13 (3%)	13 (3%)
>16 to ≤24 weeks	6 (2%)	5 (1%)
>24 to ≤48 weeks	40 (10%)	54 (13%)
>48 weeks	265 (69%)	265 (69%)

Source Data: Table 14.1

Overall the length of exposure to study drug was similar between each study group. Extent of exposure was defined as the time from first dose to last dose, not taking into account any possible treatment interruptions.

MO Comment: *The above lengths of exposure represent exposure to the full dose. The overall length of exposure to any dose was also similar between the study groups: 70% for the OAD versus 69% for the BID group.*

A total of 120 sites screened subjects and 115 sites in 10 countries treated at least one subject. The majority of subjects were enrolled and treated at study sites in the United States (Table 18)

Table 18 Distribution of Subjects According to Country

Country	ABC OAD (n = 384)	ABC BID (n = 386)
Argentina	12	5
Brazil	23	29
Canada	31	31
Denmark	11	7
Germany	15	14
Mexico	8	13
Poland	32	28
Spain	11	11
United Kingdom	13	12
United States	228	236

C. Methods and Specific Findings of Safety Review

Safety assessments for this study included monitoring AEs, serum beta human chorionic gonadotropin (β-HCG) testing of females of childbearing potential, and clinical laboratory (hematology and serum chemistry) tests. Development of drug-related toxicities sufficiently severe to warrant dose modification, interruption, or permanent discontinuation were also monitored.

Laboratory tests (including pregnancy testing) were performed at Screening, Day 1, Weeks 2, 4, 8, 12, and every 12 weeks thereafter until the last subject enrolled reached 48 weeks of treatment, premature discontinuation, follow-up, and at all unscheduled study visits. Adverse events and HIV-associated conditions were assessed at the same time points starting after the first dose of study drug on Day 1. Only SAEs related to study participation were collected prior to the first dose of study drug.

At each study visit, subjects were asked in a non-leading manner about any complaints they had since the last study visit. Details of start and stop dates, severity, causality, seriousness, outcome, and action taken with investigational products were to be documented in the subject's CRF. Adverse events were graded according to the DAIDS toxicity table or, if not listed on the toxicity table, as mild, moderate, or severe.

An AE was defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment". An SAE was defined as "any AE occurring at any dose that resulted in any of the following outcomes: death, a life threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a disability/incapacity, a

congenital anomaly in the offspring of a subject who received drug, suspected ABC HSR or other medically important events that did not meet any of the above criteria"

All AEs were coded via the GSK Optimally Linked Database (GOLD) autoencoder using the Medical Dicitionary for Regulatory Activities (MedDRA) dictionary.

ADVERSE EVENTS

Adverse events were common in study CNA30021 with 94/% of subjects in each treatment group reporting at least one AE during the conduct of the study.

Table 19 shows the most commonly reported AEs, regardless of severity, grade or perceived relationship to study drug.

Table 19 Most Common (Greater than or equal to 10% Incidence) Adverse Events (Safety Population - CNA30021)

Adverse Event	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY AE	362 (94%)	364 (94%)
Nausea	87 (23%)	89 (23%)
Dizziness	88 (23%)	82 (21%)
Insomnia	73 (19%)	85 (22%)
Diarrhea NOS[1]	66 (17%)	74 (19%)
Fatigue	58 (15%)	76 (20%)
Headache	65 (17%)	68 (18%)
Abnormal dreams	63 (16%)	60 (16%)
Rash NOS[1]	62 (16%)	57 (15%)
Nasopharyngitis	52 (14%)	55 (14%)
Depression	42 (11%)	46 (12%)
Pyrexia	42 (11%)	35 (9%)
Upper respiratory tract infection NOS[1]	42 (11%)	36 (9%)
Cough	36 (9%)	45 (12%)
Vomiting NOS[1]	32 (8%)	37 (10%)
Drug hypersensitivity[2]	36 (9%)	29 (8%)

Source Data: Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 85, Table 25 and Table 14.8
1. Not Otherwise Specified (NOS) in accordance with MedDRA coding convention
2. Includes hypersensitivity to any drug and is included in this table as an AE of special interest.

Incidences of AEs were generally comparable between treatment groups. However, the incidence of fatigue (15%) was lower in the ABC once daily group compared with the ABC twice daily group (20%).

MO Comment: *There is no obvious biological reason for the 5% difference in the rate of fatigue between the treatment groups. The remainder of the AE events and rates are not unique to ABC*

containing regimens, and are commonly observed in HIV-1 infected patients on other antiretrovial drug regimens.

MO Comment: *Some of the "preferred terms" as defined by MIDAS split terms that are clinically more meaningful when combined. Table 20 below presents all grade AEs with ≥ 10% incidence regardless of perceived relationship to study drug with preferred terms combined as deemed appropriate by the FDA review team. The table is ordered to present the AEs in descending order of frequency in the ABC OAD arm.*

Table 20 Most Common (Greater than or equal to 10% Incidence) Adverse Events (Safety Population - CNA30021)

Adverse Event	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY AE	362 (94%)	364 (94%)
Nausea	87 (23%)	89 (23%)
Dizziness/Vertigo[1]	98 (26%)	90 (23%)
Insomnia	73 (19%)	85 (22%)
Headache/Migraine	70 (18%)	72 (19%)
Diarrhea NOS[2]	66 (17%)	74 (19%)
Fatigue/Malaise	64 (17%)	81 (21%)
Abnormal dreams	63 (16%)	60 (16%)
Rash NOS[2]	62 (16%)	57 (15%)
Nasopharyngitis	52 (14%)	55 (14%)
Depression/Depressed Mood	46 (12%)	48 (12%)
Abdominal pain/gastritis[2, 3]	52 (14%)	55 (14%)
Pyrexia	42 (11%)	35 (9%)
Upper respiratory tract infection NOS[2]	42 (11%)	36 (9%)
Drug hypersensitivity[4]	36 (9%)	29 (8%)
Cough	36 (9%)	45 (12%)
Vomiting NOS[2]	32 (8%)	37 (10%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 85, Table 25

1. Represents combined MedDRA preferred terms
2. Not Otherwise Specified (NOS) in accordance with MedDRA coding convention
3. Includes MedDRA preferred terms Abdominal pain lower/Abdominal pain upper/Abdominal pain NOS/Gastritis NOS/Gastrointestinal irritation/Gastrointestinal upset.
4. Includes hypersensitivity to any drug and is included in this table as an AE of special interest.

The proportion of subjects reporting any Grade 2, 3, or 4 AEs are presented in Table 21 and 22 below. Similar to Table #, Table # presents Grade 2 –4 Adverse Events regardless of perceived relationship to study drug with preferred terms combined as deemed appropriate by the FDA review team. This table is also ordered to present the AEs in descending order of frequency in the ABC OAD arm .

Table 21 Most Common (Greater than or equal to 5% Incidence) Grade 2, 3, or 4 Adverse Events (Safety Population - CNA30021) per Applicant's Analysis

Adverse Event	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY Grade 2/3/4 AE	267 (70%)	276 (72%)
Drug hypersensitivity[1, 2]	35 (9%)	27 (7%)
Insomnia	26 (7%)	36 (9%)
Depression	25 (7%)	26 (7%)
Diarrhea NOS[3]	21 (5%)	25 (6%)
Nausea	21 (5%)	25 (6%)
Headache	21 (5%)	21 (5%)
Rash NOS[3]	21 (5%)	19 (5%)
Fatigue	20 (5%)	29 (8%)
Dizziness	19 (5%)	19 (5%)
Pyrexia	19 (5%)	13 (3%)
Abnormal dreams	15 (4%)	19 (5%)
Anxiety	12 (3%)	20 (5%)

Source Data: Table 14.10

1. There was one subject in the ABC once daily group (Subject 51804) and two subjects in the ABC twice daily group (Subjects 51113 and 51519) that reported drug hypersensitivity reaction to ABC (Grade 1, study drug related).
2. Subject 52590 in the ABC twice daily group reported drug hypersensitivity to Bactrim (not related to study drug).
3. Not Otherwise Specified (NOS) in accordance with MedDRA coding convention

Table 22 Most Common (Greater than or equal to 5% Incidence) Grade 2, 3, or 4 Adverse Events (Safety Population - CNA30021)

	ABC OAD	ABC BID
	N=384	N=386
Adverse Event	n (%)	n (%)
Subjects with ANY Grade 2/3/4 AE	267 (70%)	276 (72%)
Drug hypersensitivity[1,2]	35 (9%)	27 (7%)
Insomnia	26 (7%)	36 (9%)
Depression/Depressed Mood	27 (7%)	27 (7%)
Headache/Migraine NOS	25 (7%)	23 (6%)
Fatigue/Malaise	22 (6%)	31 (8%)
Dizziness/Vertigo	22 (6%)	22 (6%)
Nausea	21 (5%)	25 (6%)
Diarrhea NOS[3]	21 (5%)	25 (6%)
Rash NOS[3]	21 (5%)	19 (5%)
Pyrexia	19 (5%)	13 (3%)
Abdominal pain/gatritis[4]	14 (4%)	21 (5%)
Abnormal dreams	15 (4%)	19 (5%)
Anxiety	12 (3%)	20 (5%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 86, Table 26
1. There was one subject in the ABC once daily group (Subject 51804) and two subjects in the ABC twice daily group (Subjects 51113 and 51519) that reported drug hypersensitivity reaction to ABC (Grade 1, study drug related).
2. Subject 52590 in the ABC twice daily group reported drug hypersensitivity to Bactrim (not related to study drug).
3. Not Otherwise Specified (NOS) in accordance with MedDRA coding convention
4. Includes MedDRA preferred terms Abdominal pain lower/Abdominal pain upper/Abdominal pain NOS/Gastritis NOS/Gastrointestinal Irritation/Gastrointestinal upset.

The incidence of Grade 2, 3 or 4 AEs are comparable between treatment groups with slightly more drug hypersensitivity occurring on the OAD arm (9%) versus the BID arm (7%) and slightly more fatigue/malaise and anxiety occurring on the BID arm.

MO Comment: *Although the increased drug hypersensitivity on the OAD arm is not statistically significant, it may signal a trend toward increased HSR AEs with increased drug exposure. Again, the remainder of the Grade 2-4 AE events and rates are not unique to ABC containing regimens and are commonly observed in HIV-1 infected patients on other antiretrovial drug regimens.*

The proportion of subjects reporting any Grade 3 and 4 AEs are presented in Tables 23 and 24 below.

MO Comment: *The tables differ only in the number of subjects on the BID arm who experienced a Grade 3/ 4 drug hypersensitivity. Subject 51101 was misclassified by GSK as having experienced a Grade 3 ABC HSR when in fact he experienced a grade 2 ABC HSR. This change does not alter the percent or the p-value of the difference between the two arms.*

Table 23 Most Common Severe (Grades 3 and 4) Adverse Events (>1% Incidence, Safety Population - CNA30021) per Applicant's analysis

Severe (Grade 3 and 4) Adverse Events	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY Grade 3/4 AE	101 (26%)	86 (22%)
Drug hypersensitivity	19 (5%)	8 (2%)
Increased creatine phophokinase	10 (3%)	4 (1%)
Increased aspartate aminotransferase	7 (2%)	5 (1%)
Depression	6 (2%)	6 (2%)
Diarrhea	6 (2%)	0
Increased alanine aminotransferase	5 (1%)	7 (2%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 88, Table 29

Table 24 Most Common Severe (Grades 3 and 4) Adverse Events (>1% Incidence, Safety Population - CNA30021) per FDA analysis

Severe (Grade 3 and 4) Adverse Events	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY Grade 3/4 AE	101 (26%)	86 (22%)
Drug hypersensitivity	19 (5%)	7 (2%)
Increased creatine phophokinase	10 (3%)	4 (1%)
Increased aspartate aminotransferase	7 (2%)	5 (1%)
Depression	6 (2%)	6 (2%)
Diarrhea	6 (2%)	0
Increased alanine aminotransferase	5 (1%)	7 (2%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 88, Table 29

The incidence of Grade 3 and 4 AEs are comparable between treatment groups with the exception of the incidence of drug hypersensitivity and diarrhea on the OAD arm. There were 18/384 (5%) subjects with Grade 3 drug hypersensitivity events in the ABC OAD group compared to 6/386 (2%) subjects in the ABC twice daily group (p-value = 0.017). This difference is driven by Grade 3 reactions; each arm had one Grade 4 HSR. Similarly 2% of subjects on the OAD arm had severe diarrhea compared to zero subjects on the BID arm (p-value = 0.015).

MO Comment: *These differences likely represent increased exposure with the OAD dosing leading to increased allergen exposure in the case of HSRs and increased GI toxicity in the case of diarrhea. Although, this difference was observed in a small percentage of the population, it is concerning (especially the HSRs) and warrants labeling to make healthcare providers and patients aware of the risk.*

Dr. Smith performed a sensitivity analysis looking at Grade 3 and 4 AEs by gender and race. There were no significant differences or trends in the incidence of Grade 3 and 4 AEs by gender or race.

SERIOUS ADVERSE EVENTS (SAEs)

Fatal SAEs

Fatal adverse events are summarized in Table 25. None of the fatalities were considered by the investigator to be attributable to study drug.

Table 25 Fatal Adverse Events (Safety Population - CNA30021)

Fatal Adverse Events	Subject Number	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY Event		2 (<1%)	3 (<1%)
Cardiac arrest	51382	1 (<1%)	0
Azotemia[1]	51243	1 (<1%)	0
Renal failure acute		1 (<1%)	0
Sepsis NOS[2] (diabetes)	51529	0	1 (<1%)
Death NOS[2] (undetermined cause)	52701	0	1 (<1%)
Edema peripheral	52703	0	1 (<1%)
Neck mass		0	1 (<1%)
Lymphoma		0	1 (<1%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 89, Table 30
1. Investigator considered cause of death to be related to lymphoma.
2. Not Otherwise Specified (NOS) in accordance with MedDRA coding convention

There were five subject fatalities (two subjects in the ABC once daily group and three subjects in the ABC twice daily group). Subject narratives for each of the five fatalities are provided below:

- Subject 51382 (ABC once daily + 3TC + EFV) was a 66-year old male with a history of moderate chronic obstructive pulmonary disease, deep vein thrombosis, pulmonary emboli, and pulmonary hypertension. Approximately 14 months after starting study treatment, the subject developed fever, chills, shortness of breath, and a mild cough without sputum production. He was admitted to the hospital 3 days later. A chest X-ray showed infiltrates bilaterally (right greater than left), and he was started on ceftriaxone and azithromycin. He continued on the investigational products without interruption. Two days after admission his condition was improved with noted decreased shortness of breath and a decreased temperature, but a mild cough was still present. He was discharged from the hospital a week later, and while waiting for a ride home he experienced a cardiac arrest. He was pronounced dead in the hospital emergency room. No autopsy was performed. Pulmonary emboli were considered the most likely cause of death. In the investigator's opinion, the pneumonia and cardiac arrest were not related to use of the investigational products.

- Subject 51243 (ABC once daily + 3TC + EFV) was a 68-year old female with a history of non-Hodgkin's lymphoma, pyelonephritis, idiopathic thrombocytopenia, and mild Parkinson's disease. Approximately 5 months after starting the investigational product, the subject presented to the emergency room with a 5-day history of nausea, vomiting, fever, and a worsening sore throat. She was noted to have substantially enlarged, painful submandibular lymph nodes. She was admitted to the hospital for hyperuremia, acute renal failure, and complications of lymphoma

that had been in remission. Treatment with investigational products was discontinued. No further aggressive intervention was planned, and she was discharged to her home after a 5-day hospital stay. She expired the next day. In the investigator's opinion, the hyperuremia and renal failure were not related to the use of the study medications and were considered possibly attributable to the subject's lymphoma.

- Subject 51529 (ABC twice daily + 3TC + EFV) was a 38-year old male with a history of insulin dependent diabetes mellitus. At the Week 4 visit, the subject's diabetes was under control and he did not report any AEs. Approximately 3 weeks later, the subject was found dead in his hotel room while on vacation. Information obtained from the medical examiner described cellulitis of one arm and indicated that the probable cause of death was sepsis. *Klebsiella pneumoniae* was cultured from a blood culture. In the investigator's opinion, the event was unrelated to the use of study drugs. Cellulitis was considered a possible cause of the fatal sepsis.

- Subject 52701 (ABC twice daily + 3TC + EFV) was a 59-year old male. Approximately 12 months after starting the investigational products, the subject died. The coroner's report stated that the death was from "natural causes." The investigator considered there was no reasonable possibility that the death may have been caused by use of the investigational products.

- Subject 52703 (ABC twice daily + 3TC + EFV) was a 55-year old male. Approximately 2 months after initiating study treatment, the subject was hospitalized due to pneumonia. Study treatment was continued. While hospitalized, the subject was also diagnosed with lymphoma. The pneumonia resolved 2 weeks after onset. Three months after initiating study drugs, the subject was re-hospitalized due to a neck mass. He also developed a fever. Study treatment remained unchanged. Three weeks later, he was re-hospitalized due to swelling of feet secondary to chemotherapy. Treatment with investigational products was discontinued and the subject expired approximately two and a half months after the onset of the pneumonia. In the investigator's opinion, neither the pneumonia nor the fatal events of neck mass and lymphoma was related to the use of study treatment. The pneumonia was considered possibly related to the disease under study, HIV infection.

MO Comment: *This reviewer agrees that based on the information provided the deaths do not appear to be drug related.*

In addition to the above reports, GSK reported a stillbirth as another death in the ABC BID arm. Since the death of an unborn fetus is not considered a "subject fatatlity" this reviewer did not include it in the above discussion. However, details of this stillbirth can be found in the "Pregnancies" section of this review.

Non-fatal SAEs

The incidence of SAEs occurring in >1 subject is shown below in Table 26.

Table 26 Most Common (>1 Subject in Either Treatment Group) Serious Adverse Events (Safety Population - CNA30021)

Serious Adverse Event	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY SAE	66 (17%)	62 (16%)
Drug hypersensitivity[1]	36 (9%)	28 (7%)
Pneumonia NOS[2]	4 (1%)	5 (1%)
Ectopic pregnancy	2 (<1%)	0
Suicidal ideation	1 (<1%)	5 (1%)
Suicide attempt	1 (<1%)	2 (<1%)
Diarrhea NOS[2]	1 (<1%)	2 (<1%)
Dehydration	1 (<1%)	2 (<1%)
Bronchitis NOS[2]	0	2 (<1%)
Cellulitis	0	2 (<1%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 91, Table 31
1. ABC HSR events were considered SAEs regardless of severity.
2. Not Otherwise Specified (NOS) in accordance with MedDRA coding convention

Incidences of SAEs were generally comparable between treatment groups with 17% (66/384) of subjects in the ABC once daily group experiencing an SAE compared with 16% (62/386) of subjects in the ABC twice daily group. The number of subjects reporting any SAE includes reports of suspected ABC HSR that were classified as SAEs in accordance with GSK policy.

Of note, there were six reports of suicidal ideation (1 in the OAD arm and 5 in the BID arm) and three reports of suicide attempt (1 in the OAD arm and 2 in the BID arm). Two cases of suicide attempt were assessed by the investigator as related to efavirenz use. Additionally, two cases of drug-related suicidal ideation were also attributed to use of efavirenz by the investigator.

MO Comment: *Serious psychiatric events on ABC is a concern that was raised during the review of the data submitted with sNDA for traditional approval. The presence of the aforementioned suicidal ideation and attempts neither heightens nor allays those concerns. Currently, GSK is in the process of addressing the issue of a potential increased risk of acute and serious psychiatric events related to ABC use through a Phase IV commitment outlined in the ABC traditional approval letter (April 15, 2004).*

Adverse Events Leading to Premature Discontinuation of Investigational Product and /or Study

Adverse events leading to study drug discontinuation, with an incidence of greater than three subjects in either group during the conduct of study, are summarized in Table 27.

Table 27 Adverse Events Leading to Permanent Treatment Discontinuation Occurring in Greater than or equal to 3 Subjects in Either Group (Safety Population - CNA30021)

Adverse Event Leading to Study Drug Discontinuation	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Subjects with ANY AE leading to study drug discontinuation	60 (16%)	59 (15%)
Drug hypersensitivity	36 (9%)	28 (7%)
Abnormal dreams	1 (<1%)	4 (1%)
Depression	1 (<1%)	4 (1%)
Insomnia	1 (<1%)	4 (1%)
Diarrhea NOS[1]	2 (<1%)	3 (<1%)
Rash	4 (1%)	3 (<1%)
Dizziness	0	3 (<1%)

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 92, Table 32
1. Not Otherwise Specified (NOS) in accordance with MedDRA coding convention

The type and frequency of AEs leading to premature discontinuation reported in each treatment group were similar: 16% (60/384) of subjects in the ABC once daily group and 15% (59/386) of subjects in the ABC twice daily group.

The type and frequency of SAEs leading to premature discontinuation reported in each treatment group were similar: 11% (42/384) of subjects in the ABC once daily group and 9% (35/386) of subjects in the ABC twice daily group.

MO Comment: *The rate of discontinuation due to an AE is comparable to that seen in other clinical trials where ABC was the test agent.*

Other Significant Adverse Events (Hypersensitivity Reactions (HSRs))

The rates of ABC HSR as reported by the investigators are presented in Table 28.

Table 28 Summary of Reported ABC HSR (Safety Population - CNA30021)

	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
ABC HSR Cases	36 (9%)	28 (7%)

Source data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 92, Table 33

A total of 36 (9%) subjects were reported in the ABC once daily group and 28 (7%) subjects in the ABC twice daily group with suspected ABC HSR. A total of 5/384 (1%) subjects in the ABC once daily group (Subjects 51804, 51694, 52828, 51638, and 51430) and 3/386 (1%) subjects in the ABC twice daily group (Subjects 51864,

52225, and 52418) had an ABC HSR hospitalization event.

MO Comment: *Subjects are reported as having "suspected ABC HSR" because according to GSK's definition a definite ABC HSR case can only occur in someone with documented rechallenge, everyone else is probable or possible and thus suspected. The ABC HSR rate in this clinical trial is comparable to the rate in other randomized, blinded, controlled, clinical trials where the HSR rate is ascertained prospectively.*

To this reviewer's knowledge the above cases represent all of the investigator identified HSR cases and none of these cases were challenged or overruled by GSK.

GSK reports that of the subjects who experienced an HSR event, a total of 7/36 (19%) subjects in the ABC once daily group and 8/28 (29%) subjects in the ABC twice daily group reported a history of drug allergies.

MO Comment: *In this reviewer's opinion no conclusions can be drawn from the fact that in this clinical trial 19% of OAD ABC users and 29% of BID ABC users had a prior history of drug allergy. GSK does not report whether or not this information was obtained prospectively or after the HSR event. They also do not report how this compares to the subjects who did not experience an HSR.*

The most common HSR symptoms (>40% in either treatment group) included rash, fever, fatigue, malaise, head ache, nausea, and abdominal pain. Table 29 provides a summary of symptoms reported by subjects with suspected ABC HSR.

Table 29 Clinical Signs and Symptoms Associated with ABC HSR (Safety Population - CNA30021)

Symptoms Reported	ABC OAD N=36 n (%)	ABC BID N=28 n (%)
Rash	29 (81%)	20 (71%)
Fever	22 (61%)	14 (50%)
Fatigue	21 (58%)	11 (39%)
Other	21 (58%)	14 (50%)
Malaise	18 (50%)	16 (57%)
Headache	17 (47%)	7 (25%)
Nausea	16 (44%)	12 (43%)
Chills	14 (39%)	11 (39%)
Myalgia	12 (33%)	8 (29%)
Diarrhea	10 (28%)	6 (21%)
Vomiting	9 (25%)	5 (18%)
Arthralgia	8 (22%)	4 (14%)
Dyspnea	8 (22%)	6 (21%)
Cough	7 (19%)	7 (25%)

Symptoms Reported	ABC OAD N=36 n (%)	ABC BID N=28 n (%)
Tachycardia	7 (19%)	2 (7%)
Edema	5 (14%)	6 (21%)
Conjunctivitis	5 (14%)	3 (11%)
Pharyngitis	4 (11%)	5 (18%)
Other mucosal lesions	4 (11%)	1 (4%)
Hypotension	4 (11%)	0
Stomatitis	2 (6%)	2 (7%)
Abdominal pain	3 (8%)	12 (43%)
Wheezing	1 (3%)	0

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 94, Table 34

GSK reports that there is no difference in the type and frequency of HSR associated symptoms between the two arms. Dr. Smith performed a sensitivity analysis of this data and found GSK's report to be accurate with the exception that significantly more HSR associated abdominal pain occurred on the BID arm than the OAD arm.

MO Comment: *Although there is no significant difference between the rate and types of sypmtoms associated with HSR there appears to be a trend towards more symptoms on the OAD arm versus the BID arm. Of all the symptoms with increased frequency on the OAD arm the presence of more hypotension is most concerning and indicates to this reviewer that HSRs with ABC OAD may be more severe and life-threatening than with ABC BID. Again this potential increased severity in HSRs with the OAD regimen warrants mentioning in the label.*

Of note, as per the AE dataset there were three cases of hypotension on the ABC BID arm that were not related to HSR. Upon reviewing the Case Report Forms (CRF) for these three subjects, one subject was found to be mislabeled. Subject 52950's CRF reports the AE "LBP" which is transcribed in the CRF as "low back pain", but in the AE dataset as "low blood pressure" namely hypotension. No where in this subject's CRF is hypotension mentioned. Subject 52647 had "mild orthostatic hypotension" associated with an erythematous rash and left CVA tenderness on the same day. Subject 51170 had grade 3 hypotension associated with anemia, shortness of breath, pallor, productive cough, dizziness, right middle lobe rhonci, fatigue and intermittent headache. In this reviewer's opinion there appears to be only one true documented case of hypotension on the ABC BID arm. Subject 52647's orthostatic hypotension does not have the same level of seriousness or clinical significance as subject 51170's grade 3 hypotension. In any case even if the two cases of hypotension were credited to the BID arm they are distinct from the hypotensive cases observed on the OAD, since on the BID arm the hypotension was not associated with any particular illness, syndrome or constellation of symptoms and therefore represents a rare finding 2/386 (<1%). Whereas on the OAD arm, all four cases of hypotension (11%) were associated with ABC HSR.

In CNA30021 rash was the most common symptom experienced by subjects with a HSR.

MO Comment: *Similar to the results from CNA30024 (the pivotal trial in support of ABC traditional approval), rash was the most common symptom associated with HSR. Overall, in nine other clinical trials where data from HSR cases were obtained prospectively, GSK identified fever as the most common symptom associated with HSRs with rash as the second most common.*

Table 30 provides a summary of subjects with an ABC HSR rash as a symptom of the event:

Table 30 Summary of HSR Subjects Reporting Rash (Safety Population - CNA30021)

		ABC OAD N=384 n (%)	ABC BID N=386 n (%)
ABC HSR cases		36/384 (9%)	28/386 (7%)
Any rash		29/36 (81%)	20/28 (71%)
Rash only		0	1/20 (5%)
Rash with additional HSR symptoms		29/29 (100%)	19/20 (95%)
Disseminated rash		28/29 (97%)	17/20 (85%)
Localized rash		1/29 (3%)	3/20 (15%)
Maximum rash grade :	1	6 (21%)	3 (15%)
	2	16 (55%)	15 (75%)
	3	6 (21%)	2 (10%)
	4	1 (3%)	0

Source Data: Clinical Study Report CNA 30021, module 5.3.5.1, p. 95, Table 35

The OAD arm had a greater number of subjects with disseminated rash and grade 3 and 4 rash.

MO Comment: *Again the severity of the signs and symptoms associated with the HSR and therefore the HSR itself is greater on the ABC OAD arm compared to the ABC BID arm.*

Pregnancies

Eleven female subjects became pregnant during the conduct of this study. Seven subjects were randomized to the ABC OAD arm and four subjects were randomized to the ABC BID arm. The outcomes of these pregnancies are summarized below (Source data: Clinical Study Report CNA 30021, module 5.3.5.1, section 8.6, page 95):

- Subject 51179 (ABC OAD + 3TC + EFV), a 27 year old female, with a history of a tubal ligation, was found to have an ectopic pregnancy 5 weeks after starting study medication. She was instructed to discontinue study drugs but continued to take them. Her last menstrual period occurred 10 days before starting study medication, and from the dates given, she was exposed to study medication before conception and during her first trimester of pregnancy. She was hospitalized for 5 days for laparoscopic removal of the ectopic pregnancy. Study drug was subsequently discontinued. The event resolved and she was

withdrawn from the study. In the investigator's opinion, the ectopic pregnancy was not related to the use of study drugs.

- Subject 51222 (ABC OAD + 3TC + EFV), a 32 year old female, became pregnant approximately nine months after initiating investigational products. The investigational products were discontinued at that time, and the subject was discontinued from the study. Four days later, on 26 July 2002, she underwent a laparoscopy, a right salpingectomy, peritoneal lavage, and dilation and curettage due to an ectopic pregnancy, and the event was considered to be resolved on that date. The subject's recent vaginal bleeding and history of chronic thrombocytopenia were cited as factors that may have impacted the outcome of the pregnancy. The investigator considered the ectopic pregnancy to be severe and serious because it required a surgical procedure. The investigator did not consider the event to be related to use of the investigational products.
- Subject 51813 (ABC OAD + 3TC + EFV), a 39 year old female, became pregnant approximately 15 months after the subject started on investigational product (pregnancy tests performed at discharge from the study were positive). The subject underwent an ultrasound approximately one month later; and the investigator conceded that, at 5 weeks 3 days gestation, it was too early to determine whether any birth defects were present. Treatment with prescribed ART was continued uninterrupted. Her last menstrual period occurred approximately one week prior to discontinuing investigational product, and from the date given, she was exposed to investigational products for approximately 15 months before conception and until one week gestation. The outcome is pending and the expected delivery date is 25 November 2003.
- Subject 51018 (ABC OAD + 3TC + EFV), a 37 year old female, became pregnant following initiation of the investigational products, and underwent an elective abortion on 20 November 2001. The investigational site was not informed about the pregnancy until 02 January 2002 at which time a postive serum beta HCG result was detected for the subject. The investigational products were initially interrupted as the investigator was not aware of the subject's abortion. Another quantitative beta HCG test was requested for verification of the terminated pregnancy. The subject was allowed to remain on study and continue on the investigational products.
- Subject 52754 (ABC OAD + 3TC + EFV), a 25 year old female, became pregnant approximately 9 months after initiating use of the investigational products. The date of her last menstrual period was 2 months earlier, on 16 August 2002, and she stopped treatment with the investigational products on 23 September 2002. The subject was withdrawn from the study. The estimated date of delivery was 16 May 2003. On 09 May 2003, she gave birth to a normal female neonate (7lb. 7 oz.) by vaginal delivery.
- Subject 51672 (ABC OAD + 3TC + EFV), a 24 year old female, became pregnant approximately 11 months after starting investigational product. Her last menstrual period occurred approximately 11 months after starting investigational product and, from the dates given, she was exposed to investigational product before conception, and the estimated due date was 11 September 2003.

- Subject 51638 (ABC OAD + 3TC + EFV), a 32 year old female, began treatment on 30 January 2002. ABC was stopped after 6 days of treatment due to a suspected ABC hypersenstivity reaction. She was subsequently started on stavudine (d4T, Zerit ƒ) in combination with 3TC and EFV. Liver function test monitoring performed approximately 7 months after initiation of the investigational products, revealed an elevated alanine transaminase value of 618 and an elevated aspartate transaminase value of 477. Treatment with 3TC, EFV, and d4T was interrupted at that time, and the subject was subsequently diagnosed with Hepatitis C. On 19 September 2002, a urine pregnancy test was positive. She was referred to a gynecologist for serial serum HCG testing and test results confirmed a spontaneous abortion. In the investigator's opinion, there was no reasonable possibility that the event may have been caused by use of the investigational products.
- Subject 52849 (ABC BID + 3TC + EFV), a 25 year old female, became pregnant approximately 1 year after starting the investigational products. No prenatal testing was performed to detect birth defects. On 29 January 2003, treatment with the investigational products was discontinued. On 21 February 2003, the subject underwent an elective abortion.
- Subject 53040 (ABC BID + 3TC + EFV), a 32 year old female, became pregnant approximately 5 months after initiating use of the investigational products. Treatment with investigational products was discontinued and the subject was withdrawn from the study. Her last menstrual period occurred 5 months after starting study medication and, from the dates given, she was exposed to study medication before conception and through the fifth week of gestation. The estimated due date was 21 April 2003. Follow-up is being conducted with the investigator to determine the outcome of the pregnancy.
- Subject 52907 (ABC BID + 3TC + EFV), a 19-year old female, became pregnant 7 months after starting investigational product. All investigational products were discontinued and she was withdrawn from the study. Her last menstrual period occurred approximately 6 months after starting the investigational products, and from the dates given, she was exposed to study medication before conception and until approximately 6 weeks gestation. She gave birth to a healthy, female neonate in an uncomplicated delivery. The neonate tested negative for HIV. Per the investigational site's contact with a nurse at the obstetrics clinic, the neonate died approximately 1 month after delivery (the exact date of death was unspecified) due to sudden infant death syndrome. The investigational site was unable to obtain official confirmation of the death with supporting hospital records. Study site staff contacted all hospitals in the subject's county of residence and found no record of a SIDS death for a female infant. All attempts to locate the subject were unsuccessful. In the investigator's opinion, there was no reasonable possibility that the infant death was related to the use of the investigational products.
- Subject 51818 (ABC BID + 3TC + EFV), a 29 year old female, became pregnant at an unspecified time after commencing investigational product. Treatment with investigational products was consequently discontinued and the subject withdrawn from study. The subject underwent planned termination approximately 1 month later. The subject also wished to continue on study, as such investigational products were subsequently recommenced on an unspecified date

following re-entry into this protocol. No further information was available at the time of reporting.

GSK provided the following pregnancy outcome information for the three subjects, whose pregnancies were ongoing at the time this sNDA was submitted:

- Subject 51672, whose estimated due date was 11 September 2003. Staff at the investigational site later learned that the subject gave birth to a neonate, but details concerning the birth (i.e., the delivery date, type of delivery, gender of the neonate, health status of the neonate, etc.) could not be confirmed with the study subject. The site staff made many attempts to have the subject return to the office for a follow-up visit and to obtain information on the birth via telephone without success. The subject was considered lost to follow-up.
- Subject 51813, whose expected due date was 25 November 2003. Follow up was received which specified that the subject had elected to terminate her pregnancy in April 2003 (the exact date was unknown), approximately two months after the date of her LMP and approximately one month after ultrasound. The subject continued on her prescribed ART (abacavir, lamivudine and efavirenz) after the abortion. No further information was provided at the time of reporting.
- Subject 53040, whose expected due date was 21 April 2003. The subject had an uneventful pregnancy, but it was noted that glucose intolerance was identified. She received treatment with zidovudine, lamivudine, and nelfinavir and showed good tolerance to this treatment regimen. On 24 April 03 at 40 weeks gestation, the subject gave birth to a normal female neonate via an elective cesarean section that included administration of parenteral zidovudine during the surgical procedure. At the time of birth, the neonate's weight was 2860 grams, length 47 cm, cephalic perimeter of 34 cm, Apgar score 9/9, and Silverman score was zero. The subject had a normal postsurgical evolution. The neonate received oral zidovudine, 2 mg per kilogram, every 6 hours over a six-week period. Follow-up on the female infant conducted in October 2003 revealed no evidence of HIV infection, but she is receiving cisapride and ranitidine due to esophageal reflux.

MO Comment: *There was no significant difference between the number of pregnancies that occurred on each arm. EFV is part of the background regimen in both arms of the study, and a warning and caution in the label discourage its use in women who are pregnant or trying to become pregnant. Based on the narratives above and the background rate of spontaneous abortion and SIDS it is not clear if one or more of the study drugs were related to the pregnancy outcomes.*

Clinical Laboratory Findings

The applicant provided summary statistics of measured results and change from baseline for each hematology and clinical chemistry parameter.

Neither the ABC nor the ZDV treatment groups had significant changes in their median clinical chemistry values over 48 weeks of treatment. Median changes from baseline in all clinical chemistry parameters were generally small and comparable between the

treatment groups (Table 31).

Table 31 Baseline and Median Changes from Baseline in Chemistry Laboratory Values

	ABC OAD + 3TC + EFV		ABC BID + 3TC + EFV	
Chemistry Parameters	Baseline values	Median Change at Week 48	Baseline values	Median Change at Week 48
AL T (U/L)	29.0	-3.0	28.0	-2.0
AST (U/L)	28.0	-6.0	28.0	-4.0
Albumin (g/L)	41.0	2.0	41.0	1.0
Alkaline phosphatase (U/L)	73.0	11.0	73.0	15.0
Amylase (U/L)	73.0	-4.0	72.0	-3.0
Pancreatic amylase (U/L)	43.0	-15	54.0	n/a
Bicarbonate (µmol/L)	24.0	-1.1	24.1	-1.3
Bilirubin (µmol/L)	7.0	-2.0	7.0	-2.0
Chloride (mmol/L)	104.0	2.0	104.0	2.0
Cholesterol (mmol/L)	4.2	0.9	4.1	0.8
CPK (U/L)	90.5	12.0	87.0	13.0
Creatinine (µmol/L)	80.0	0	76.0	-0.5
Glucose (mmol/L)	5.1	0.3	5.0	0.3
Potassium (mmol/L)	4.2	0	4.2	0
Sodium (mmol/L)	141.0	1.0	141.0	0
Triglyceride (mmol/L)	1.5	0.2	1.4	0.3

Source data: Tables 14.27 and 14.28,Clinical Study Report, CNA300021,module 5.3.5.1, p. 656-687

There were no significant differences in median baseline chemistry values or median change in chemistry values between the two treatment groups.

MO Comment: *The Week 48 values for median change in pancreatic amylase values were not available. GSK did not provide an explanation for this in the study report; however, based on the data provided there is no difference in the rate of subjects with pancreatic enzyme increase in the two groups (OAD – 8; BID -- 10) and the number of subjects who had pancreatic amylase measured was very low (n=6 in the OAD group and n=6 in the BID group).*

Table 32 Median Baseline and Changes from Baseline in Select Hematology Laboratory Values

	ABC (OAD) + 3TC + EFV		ABC (BID) + 3TC + EFV	
Hematology Parameters	Baseline values	Median Change at Week 48	Baseline values	Median Change at Week 48
Hemoglobin (g/L)	142	5.0	142	6.0
Platelets (GI/L)	221	27	223	26
RBC (TI/L)	4.8	-0.20	4.8	-0.90
WBC (GI/L)	4.76	0.41	4.87	0.57

	ABC (OAD) + 3TC + EFV		ABC (BID) + 3TC + EFV	
Hematology Parameters	Baseline values	Median Change at Week 48	Baseline values	Median Change at Week 48
Neutrophils absolute – conv unit (GI/L)	2.55	0.55	2.49	0.67
Lymphocytes (%)	35.0	-0.7	34.6.	-1.4
Monocytes (%)	6.3	-0.7	6.4	-0.7
Eosinophils (%)	2.1	0.1	2.4	-0.1

There were no significant differences in median baseline hematology values or median change in hematology values between the two treatment groups.

Grade 3 and 4 treatment-emergent abnormalities are summarized in Table 33.

Table 33 Grades 3 and 4 Treatment-Emergent Laboratory Abnormalities (Safety Population - CNA30021)

Grades 3 and 4 Laboratory Abnormalities	ABC OAD N=384 n (%)			ABC BID N=386 n (%)		
	Gr 3	Gr 4	Gr 3-4	Gr 3	Gr 4	Gr 3-4
Clinical Chemistry						
Elevated ALT	14 (4%)	9 (2%)	23 (6%)	18 (5%)	6 (2%)	24 (6%)
Elevated AST	10 (3%)	13 (3%)	23 (6%)	9 (2%)	5 (1%)	14 (4%)
Alkaline phosphatase	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Amylase	13 (3%)	2 (<1%)	15 (4%)	12 (3%)	0	12 (3%)
Bilirubin	0	2 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)
Creatine phosphokinase	13 (3%)	31 (8%)	44 (12%)	13 (3%)	22 (6%)	35 (9%)
Creatinine	0	0	0	0	1 (<1%)	1 (<1%)
Glucose	4 (1%)	1 (<1%)	5 (1%)	5 (1%)	1 (<1%)	6 (2%)
Sodium	2 (<1%)	0	2 (<1%)	1 (<1%)	0	1 (<1%)
Triglycerides	13 (3%)	5 (1%)	18 (5%)	13 (3%)	8 (2%)	21 (6%)
Hematology						
Hemoglobin	0	8 (2%)	8 (2%)	0	2 (<1%)	2 (<1%)
Neutrophils absolute	6 (2%)	3 (<1%)	9 (2%)	4 (1%)	1 (<1%)	5 (1%)
Platelets	2 (<1%)	0	2 (<1%)	2 (<1%)	0	2 (<1%)
WBC	0	0	0	1 (<1%)	0	1 (<1%)

Source Data: Table 36, Clinical Study Report, CNA300021,module 5.3.5.1, p.99

Incidences of specific treatment-emergent Grade 3 or 4 clinical chemistry and hematology abnormalities were generally low and comparable between treatment groups. There were 44 (12%) subjects in the ABC once daily group and 35 (9%) subjects in the ABC twice daily group who had treatment abnormal Grade 3 and 4 creatine phosphokinase (CPK) laboratory values. A sensitivity analysis by Dr. Smith showed a significant association in Grade 2-4 increases in ALT,

Grade 3-4 increases in AST and the occurrence of any Grade 3 –4 AE and subjects who had elevated CPK levels compared to subjects who did not have CPK elevations.

MO Comment: *The 12% Grade 3 and Grade 4 creatine phosphokinase levels in the OAD arm are slightly higher than that in the comparator ABC BID group and in other ABC BID dosing groups in other clinical studies. These numbers do not correlate with any specific clinical adverse event, however, they do correlate with an increased incidence of any Grade 3-4 AE.*

The frequency of individual treatment-emergent clinical chemistry abnormalities was similar between males and females with the exception of creatine phosphokinase. Males in the ABC OAD group had a higher frequency of Grade 3 and 4 creatine phosphokinase (12%) compared with females (8%); likewise, males in the BID had a higher frequency of Grade 3 and 4 creatine phosphokinase (11%) compared with females (0 subjects).

Otherwise clinical chemistry abnormalities for males and females were generally comparable to the overall Safety Population in both the ABC OAD and the ABC BID treatment groups. However, there was a higher proportion of females on the OAD group versus the BID group with grade 1 (89% vs 74% respectively), grade 2 (42% vs 30% respectively), grade 4 (10% vs 4% respectively) and grade 3 + 4 (21% vs 14% respectively) any treatment emergent chemistry abnormalities. Similarly females on the OAD arm had more grade 3 (5%) , grade 4 (2%) and grade 3+4 (7%, n = 4) hematology abnormalities versus 0% on the BID arm.

MO Comment: *Overall, the total number of female subjects was small, moreover, the number of female subjects on the OAD arm was less compared to the BID arm. Given that these were unplanned subgroup analyses and that the sample size for the OAD female group is small in comparison to the BID group, the observed differences are likely to have very little clinical significance.*

D. Adequacy of Safety Testing

The 48 week safety data collected in Study CNA30021 significantly adds to the overall knowledge of ABC's safety profile in HIV treatment naïve subjects, and supports the application for traditional approval of once daily dosing of ABC.

E. Summary of Critical Safety Findings and Limitations of Data

This supplement presents an adverse event profile for ABC that is not significantly different than that noted during the accelerated and traditional NDA reviews, with the exception of more significant HSR and diarrhea in the OAD arm.

The most common adverse events reported in conjunction with ABC OAD use were nonspecific (namely, nausea, dizziness, insomnia, diarrhea, fatigue) events that were seen as commonly with BID dosing and are also commonly with other NRTIs, antiretrovirals and HIV-1 disease.

ABC HSRs were reported by investigators at a rate of 9% for the ABC OAD arm and 7% for the ABC BID arm. Grade 3 and Grade 4 ABC HSRs were significantly higher in the OAD arm (n=19, 5%) than in the BID arm (n=7, 2%) with a p value of 0.017. Although the numbers are small, more severe ABC HSRs on the OAD arm indicates increased toxicity as the exposure increases. This potential increased toxicity warrants continued evaluation of identifiable risks factors associated with HSR, so that healthcare providers may more safely prescribe ABC. Severe diarrhea was also more common on the OAD arm (n=6, 2%) than on the BID arm (n=0).

The pattern of laboratory abnormalities in subjects receiving ABC in CNA30021 was similar to that seen with other antiretroviral drugs. Rare grade 3 and 4 elevations were seen in serum ALT, AST, amylase, bilirubin, creatine kinase (CPK), creatinine, glucose, sodium and triglycerides. Grade 3 and 4 declines were seen in neutrophils, lymphocytes, red blood cells and platelets. None of the laboratory abnormalities were unexpected, and the frequency and severity were similar between the two treatment groups.

VIII. Dosing, Regimen, and Administration Issues

GSK is recommending a new dose of 600mg once daily with or without food. The purpose of this supplement is to establish the non-inferiority of ABC 600mg OAD compared to the adult approved dose of ABC 300mg BID with or without food. GSK did not submit a pharmacokinetic study evaluating 600mg once daily levels of intracellular carbovir triphosphate (the active metabolite of ABC). Instead GSK submitted a PK study (CNA10905) of ABC dosed at the approved 300mg BID that demonstrated a prolonged intracellular carbovir triphosphosphate terminal half-life of 20.64 hours, which supported the clinical investigation of the use of ABC OAD for the treatment of HIV infected patients (see Appendix B for a detailed review of CNA10905 by Dr. Belen).

ABC OAD is not recommended for children or patients with any degree of hepatic impairment.

IX. Use in Special Populations

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

The applicant and FDA review team independently performed a subgroup analysis of the primary efficacy endpoint by gender and found no significant difference in the response rates between males and females in either treatment group.

The applicant provided summary information for Grade 3 and 4 treatment emergent adverse events and all grade treatment emergent laboratory abnormalities by gender. Grade 3 and 4 treatment emergent adverse events were slightly higher for both males (27%) and females (25%) on the OAD arm versus the BID arm (males, 23% and females, 18%). In terms of treatment-emergent clinical laboratory abnormalities, overall males had more grade 1 – 4 "any chemistry

treatment-emergernt abnormalities" as compared to females. Males and females had similar rates of treatment emergent hematology abnormalities.

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

Both the applicant and Dr. Smith performed subgroup analyses for the primary efficacy endpoint based on race and ethnicity and found no statistically significant difference in response rates between the different racial and ethnic groups. Additionally, Dr. Smith performed a subgroup analysis for the primary efficacy endpoint based on age using a cutoff of 35 years. There was a significant treatment by age interaction ($p=0.018$) with subjects ≤ 35 years of age having an inferior response rate on ABC OAD compared to ABC BID (please see Dr. Smith's review for further details).

According to Dr. Smith " [the] median age was used to divide patients into two subgroups. ABC OAD was only non-inferior to ABC BID in older patients (>35 years of age). In CNA30024 (pivotal study for ABC traditional approval), ABC BID was only non-inferior to zidovudine in younger patients ($\leq$35 years of age). Due to the multiple interaction tests that were carried out, this finding needs to be interpreted with caution and needs to be substantiated in future studies."

MO Comment: *There is no obvious reason why younger subjects (namely, $\leq$ 35 years of age) would respond less well than older subjects to ABC OAD. The fact that overall the analysis of subjects on ABC OAD is non-inferior means that > 35 year old ABC OAD subjects did better than > 35 year old ABC BID subjects. This appears to be a chance statistical phenomenon that does not have any significant clinical impact.*

C. Evaluation of Pediatric Program

GSK did not submit any pediatric data with this supplement. ABC is currently labeled for treatment of pediatric patients from age 3 months through 13 years based on the results of pharmacokinetic studies and CNA3006, a randomized, double-blind study comparing ABC 8 mg/kg twice daily + 3TC 4 mg/kg twice daily + ZDV 180 mg/m^2 versus 3TC 4 mg/kg twice daily + ZDV 180 mg/m^2. ABC exists in an oral suspension as well as tablet form.

GSK has completed a single-dose PK study in adolescents (PACTG1018); the study report is pending. GSK initiated a PK study in neonates (PACTG 321), however, the study was terminated due to slow enrollment.

As part of the traditional approval phase IV commitments, GSK agreed to submit a summary of their Pediatric Program including study reports for PACTG 1018 (a study of ABC in adolescent subjects), ACTG 321 (a study of ABC in neonatal subjects), and an updated summary of the clinical pharmacology, safety and efficacy of abacavir in pediatric patients.

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review.

D. Comments on Data Available or Needed in Other Populations

There are no safety or efficacy data of ABC 's use in subjects with renal or hepatic impairment. However, there is a single-dose PK study involving nine healthy subjects and nine subjects with mild hepatic impairment. The 9 subjects with mild hepatic impairment experienced an 89% mean increase in AUC and a 58% mean increase in half-life. Based on these results GSK recommends that patients with mild hepatic impairment dose ABC at 200mg BID. ABC is not recommended for use in subjects with moderate or severe hepatic impairment. ABC is minimally excreted by the renal system; therefore impaired renal function is not expected to impact the PK of ABC.

Approximately 15% of the subjects in CNA30024 were co-infected with Hepatitis B, Hepatitis C or in less than 1% both Hepatitis B and C. A subgroup analysis showed that the virologic response rate was lower in the co-infected subjects (ABC arm, 57% and ZDV arm, 59%) than in the non co-infected subjects (69% on both arms). However, the sample size was small, and these subjects as part of the enrollment criteria had to have relatively normal liver enzymes and no evidence of clinically active hepatitis. All of the above makes it difficult to 1) draw any conclusion from these results and 2) to extrapolate these results to a population with active liver disease.

MO Comment: *No further dosing information is expected or required in subjects with renal or hepatic impairment.*

Since ABC is contraindicated in patients with moderate to severe hepatic impairment and requires dose reduction in patients with mild hepatic impairment, the fixed dose combination of ABC/3TC is contraindicated in subjects with any degree of hepatic impairment.

X. Conclusions and Recommendations

A. Conclusions

The ABC review team concurs that the clinical efficacy and safety data presented in this supplement support GSK's application for the new dosing regimen of ABC 600mg OAD. The pivotal study CNA30021 provides evidence of ABC OAD non-inferiority to ABC BID in HIV-1 antiretroviral naïve subjects.

Overall the safety profile for ABC OAD is similar to ABC BID. The only significant difference was a higher incidence of severe HSR and diarrhea associated with ABC OAD. The remainder of the treatment-emergent adverse events presented in this supplement occurred with similar frequency on the ABC BID arm.

B. Recommendations

From the clinical perspective this sNDA can be approved. Review of the data from CNA30021 provides evidence of effectiveness and safety sufficient to support the new dosing regimen of 600mg OAD.

GSK proposed significant revisions to the most recently approved product label for ABC 300mg BID (April 15, 2004). After negotiations with DAVDP, GSK and DAVDP agreed upon a final label. The major revisions are described below:

1. The MICROBIOLOGY section was rearranged to conform to the format used in other NRTI drug labels. Additional information regarding the K65R mutation and cross-resistance with other NRTIs has been included in the Cross Resistance subsection.

2. The CLINICAL PHARMACOLOGY section was updated to include a description of CNA10905 study results.

3. The INDICATIONS AND USAGE Section was updated to include a usage statement regarding more severe HSR on OAD ABC. This section was also updated to include a description of study CNA30021 and study results in the Clinical Studies subsection, the Adverse Reactions subsection and the Laboratory Abnormalities subsection.

4. The CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, MEDICATION GUIDE AND WARNING CARD were all updated to include strengthened HSR wording.

XI. Appendix

A. Other Relevant Materials

Not applicable

B. Individual More Detailed Study Reviews (If performed)

STUDY CNA 10905
Reviewed by: Ozlem Belen, MD

Title: An open label, single arm, pharmacokinetic study of abacavir and its intracellular anabolite carbovir triphosphate following chronic administration of an abacavir 300 mg BID containing regimen (Ziagen or Trizivir) in HIV infected patients.

OBJECTIVES

Primary Objective

To describe the intracellular pharmacokinetics of carbovir triphosphate (CBV-TP) at steady-state following administration of an abacavir 300 mg BID containing regimen (Ziagen or Trizivir) in HIV infected patients.

Secondary Objective

To describe the pharmacokinetics of abacavir, and its relationship to triphosphate, at steady state following administration of an abacavir 300 mg containing regimen (Ziagen or Trizivir) in HIV infected patients.

RATIONALE

Supportive data for indicating once-a-daily dosing of abacavir is the goal. The pharmacokinetic data is aiming to characterize intracellular CBV-TP PK which is an active moiety of abacavir. This study was planned to confirm prolonged triphosphate CBV-TP concentrations throughout a 24-hour washout period following a multiple dosing by using a validated (LC/MS) assay.

STUDY DESIGN

This was an open-label, single arm, pharmacokinetic, pilot study in HIV infected patients who were currently on a stable abacavir-containing regimen. Screening evaluations were performed in an outpatient setting between 30 and 7 days prior to study initiation-Day 1.

Patients meeting entry criteria were entered into the study the evening prior to a 24-hour PK sampling and stayed in the clinic until the morning of Day 2, after the 24-hours PK sampling. Abacavir (Ziagen) of 300 mg BID dosing was given (approved dose).

Subjects took their normal abacavir-containing regimen the evening prior to PK sampling (Day-1), while under the supervision of clinic staff. On the day of PK sampling (Day 1), the morning dose of abacavir was taken under the supervision of clinic staff as well.

MO Comment: *It is important to note that the measurement of intracellular pharmacokinetics of carbovir triphosphate (CBV-TP is measured after at least 42 days of 300mg BID of abacavir prior to study entry in this protocol) is different from the intended/proposed once a day dosing of 600mg PO QD. Subjects were already on a steady dose regimen of 300 mg BID for at least 42 days prior to study entry and thus the PK levels were measured at the steady state of BID dosing. Subjects received 300 mg PO in the morning of the study to analyze the CBV-TP throughout the 24 hour period; the evening dose was not administered.*

STUDY POPULATION

Inclusion Criteria

Subject was eligible if all criteria applied:

- Male or female, HIV-infected subjects (documented);
- Subjects were on a stable abacavir-containing regimen (Ziagenor Trizivir);
- Ages 18 to 55 years inclusive;
- Informed consent to be provide willingly to participate in the study;
- Tobacco use was withheld for at least 24-hours before Day 1 through Day 2;
- Alcohol use was withheld for at least 24-hours before Day 1 through Day 2;
- Hypersensitivity: tolerating current abacavir-containing regimen without any symptoms consistent with hypersensitivity
- Subjects could continue all of their current HIV therapy including other nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors.

Exclusion Criteria

- Patients who had received an abacavir-containing regimen 300 mg BID for < 42 days;
- Patients with a CD4 cell count <300 cell/uL;
- Blood Donation: Blood donation (1 pint whole blood) or other significant blood loss 56 days preceding the screening phase of the study;
- Previous Study Participation in other experimental drug trial(s) in 30 days preceding the screening phase of the study;
- Drug Abuse: Subjects with active substance abuse or unexplained presence of one or more drugs of abuse detected in urine at screening;
- Clinically significant finding on screening ECG;
- Positive HCV Antibody or HepBsAg (Hepatitis B surface antigen) test at screening;
- Hemoglobin <12g/dL or platelet count <50000/μL;
- Liver function tests (AST, ALT, AlKP, LDH) >3 times the upper limit of normal, or bilirubin >2;
- Positive pregnancy test;
- Preceding Illness: Poor general health preventing fasting or blood sampling, or any acute illness within seven days prior to dosing that would, in the judgment of the investigator, interfere with participation in the study;
- Medical Condition: Within the judgment of the Principal Investigator and the Sponsor, any clinically significant disorder; predisposing condition that might interfere with absorption, distribution, metabolism, and/or excretion of drugs;
- Vaccines: As vaccines may cause a temporary increase in viral load, vaccines were not to be given within seven days of screening until discharge from the clinic;
- Chronic Medication: Subjects who chronically used any over-the-counter (OTC) or prescription medication (except vitamins) were not to change the regimen or switch their medication within 3 days of drug administration and until discharged from the study;

- Concurrent therapy with hydroxyurea, mycophenolate, or ribavirin: Subjects who were not able to discontinue use of hydroxyurea, mycophenolate, or ribavirin therapy no later than 14 days prior to entering the study;
- Psychiatric Disease: Subjects with a history of any psychiatric illness, which could impair their ability to provide informed consent;
- Ethanol Abuse: Subjects with a history of clinically significant abuse of alcohol;
- Non-compliance: Those who, in the opinion of the Principal Investigator, had a risk of non-compliance with the study procedures;

Protocol Deviations

Two subjects in Regimen 2 (354962 and # 54963) had an active substance abuse or unexplained presence of an active substance abuse or unexplained presence of one or more drugs of abuse detected in the urine at screening.

Subject # 54965 (Regimen 1) had CD4+ cell count < 300cells/ul (298 cells/ul) and all other parameters were within limits.

Sample Size and Demographics

Twenty male and/or female subjects aged 18-55 with HIV-1 who were currently on a stable abacavir-containing regimen were enrolled. No formal power calculations were performed. There were no treatment comparisons.
No subjects withdrew form the study. Nine subjects were on a current stable regimen of ZIAGEN, abacavir 300 mg BID (Regimen 1) and 11 subjects were on a current stable regimen of TRIZIVIR, abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg BID (Regimen 2).
Overall, more males (12 subjects) than females (8 subjects) and more Whites (14 subjects) than Blacks (4 subjects) or Hispanics(2 subjects) were enrolled. Ages ranged 29 to 55 years (mean age= 40.6). Body weights ranged from 53.4-131.9 kg, and heights from 156-183 cm. Total CD4+ cell counts ranged from 298-1133 cells/mm^3. CD4+ cell counts percent ranged from 15.0-50.0%, with a median of 30.15%.

ANALYSES

Clinical Evaluations

- Concomitant medications
- Adverse event inquiry
- Physical examination
- Vital signs

Laboratory Evaluations

- Plasma HIV-RNA
- Hematology panels
- Clinical chemistry panel

- Urinalysis

Safety Population
All subjects enrolled into the study who received at least one dose of current regimen were included.

Pharmacokinetic Population

The PK population included all subjects who underwent plasma PK sampling during the study. Subjects for whom one plasma PK sample was obtained and assayed were included in the summary of concentration-time data.

Two sets of blood for plasma abacavir and intracellular CBV-TP were collected over a 24-hour period as follows: pre-dose (within 30 minutes prior to dose), and 2, 4, 8, 12, 16, and 24-hours after dosing.

RESULTS

Only descriptive summary statistics were provided for intracellular CBV-TP and plasma abacavir PK parameters $AUC0\text{-}_{24,ss}$, $C_{max,ss}$, $C_{24,ss}$, $t_{max,ss}$, apparent elimination rate constant (λ_z), apparent half-life ($t_{1/2}$). Selected plasma abacavir PK Parameter estimates are summarized:

Parameter	Geometric Mean (N=20)	95%
$AUC_{0\text{-}24,ss}$, (µg*h/mL)	2.56	2.13 - 3.06
$C_{max,ss}$, (µg*h/mL)	0.88	0.75 - 1.03
$t_{1/2}$	2.59	2.04 - 3.29
$T_{max,ss}$, [a] (h)	2.00	2.0 - 3.92

- Terminal half-life observed in this study was slightly longer with a geometric mean of 2.59 (in comparison to 1.5 previously reported).

Intracellular CBV-TP PK Parameters

Parameter	**Geometric Mean (N=20)**	**95%**
$AUC_{0\text{-}24,ss}$, (fmol*h/10^6/cells)	252.78	190.05-336.21
$C_{max,ss}$, (fmol*h/10^6/cells)	29.66	22.07-39.86
$t_{1/2}$ (h)	20.64	16.39-25.99
	Median	**Min-Max**
$C_{tau,ss}$ (C12), (fmol/106 cells)	18.1	4.7-51.6
C_{24}, (fmol/10^6 cells)	16.35	3.1-61.1
$t_{max,ss}$, h	2.00	0.00-12.00

- The intracellular CBV-TP concentration profile showed steady state from 8-12 hours to 24 hours (resulting in a prolonged terminal half-life).

MO Comment: *The intracellular CBV-TP concentration time profile demonstrated a flat terminal curve from approximately 8-12 hours through 24 hours. The prolonged intracellular CBV-TP terminal half-life of 20.64 hours supports the clinical investigations on the use of abacavir once daily for the treatment of HIV infected patients. However, although this study suggests that it is reasonable to look at once a day dosing, clinical studies will have to determine whether once daily abacavir is effective at the proposed dose of 600mg QD.*

Adverse Events

Serious adverse events were defined as:
1. Death
2. Life-threatening
3. Disability/incapacity
4. Congenital anomaly/birth defect
5. Hypersensitivity reaction to abacavir

The events or outcomes listed in the Centers for Disease Control and Prevention (CDC) Classification System for HIV Infections were recorded in the "HIV-Associated Conditions" case report form (CRF) page; these outcomes, signs, symptoms, diagnosis, illness or clinical laboratory abnormality were not reported to the sponsor unless certain previously defined conditions were met.
The intensity of each AE and SAE recorded in the CRF was assigned according to the Division of AIDS criteria (NIH, NIAID, Division if AIDS). If an outcome was not listed in these criteria, intensity was assessed and the outcome was assigned mild, moderate, or severe intensity grading. After inital AE/SAE report, the investigator was required to proactively follow each subject to provide further information to the sponsor on the subject's condition.
All 8 adverse events reported resolved except for two: a case of post nasal drip and another case of mild cough with phlegm. Only one case of grade 2 severity was noted and this was phlebitis of the arms.

Adverse Events Reported

Adverse Event	**Regimen 1 N=9**		**Regimen 2 N=11**		**Total N=20**	
	No.	n(%)	No.	n(%)	No.	n(%)
No. (%) Subjects Reporting at least one AE	5	3(33%)	1	(9%)	6	4(20%)
Phlebitis of arm(s)	0	0	1	1(9%)	1	1(5%)
Postnasal drip	1	1(11%)	0	0	1	1(5%)
Discharge of eyes(s)	1	1(11%)	0	0	1	1(5%)
Eye redness	1	1(11%)	0	0	1	1(5%)
Odontalgia	1	1(11%)	0	0	1	1(5%)
Productive cough	1	1(11%)	0	0	1	1(5%)

Regimen 1 = ZIAGEN (300 mg abacavir) BID plus other antivirals in current regimen
Regimen 2 = TRIZIVIR (300mg abacavir/150mg lamivudine/300mg zidovudine) plus other antivirals in current stable regimen

No.= Number of events; n= Number of subjects experiencing the event; %= Percent of subjects experiencing event

MO Comment: *No significant laboratory values for Urinalysis, hematology or chemistry values were reported during the study. No serious adverse events or deaths were reported during this study. It is important to note that abacavir was administered at 300 mg BID regimen which is currently approved. One cannot extrapolate safety profile of 600mg once daily regimen from this study.*

CONCLUSIONS/COMMENTS

1. This was a pharmacokinetic study of abacavir and its intracellular anabolite carbovir triphosphate, to evaluate once daily dosing regimen of abacavir. There was no efficacy analysis performed.
2. The prolonged intracellular CBV-TP terminal half life of 20.64 hours supports clinical studies looking into once daily regimen for treatment of HIV infected patients.
3. After administration of 300mg dose of abacavir, CBV-TP held levels with long terminal half life at steady-state following administration of an abacavir 300 mg BID containing regimen. Clinical data is needed to determine the effectiveness of 600mg once daily dosing regimen.
4. No significant adverse event profile was noted during the study period. No serious adverse events or deaths were reported during this study. Abacavir was administered at 300 mg BID regimen which is currently approved. One cannot extrapolate safety profile of 600mg once daily regimen from this study.

REFERENCES

Bartlett, et al. Overview of the effectiveness of triple combination therapy in antiretroviral-naïve HIV-1 infected adults. AIDS 2001, 15:1369-1377

Carmona A, et al. Factors influencing survival in HIV infected patients treated with HAART. [Abstract]. Presented at the XIII International AIDS Conference, August 2003.

Farthing C, Khanlou H and Yeh V. Early virologic failure in a pilot study evaluating the efficacy of abacavir, lamivudine and tenofovir in the treatment naïve HIV-infected patients [Oral presentation Abstract 43]. Presented at The 2nd IAS Conference on HIV Pathogenesis and Treatment. Paris, France. July 2003.

Paterson D, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Annals of Internal Medicine 2000, 33:21-30.

Vibhagool. Abacavir/Combivir (ABC/COM) is comparable to indinavir/Combivir (IDV/COM) in HIV-1 infected antiretroviral therapy naïve adults: results of a 48 week open-label study (CNA3014). [Poster 063]. The 1st IAS Conference on HIV Pathogenesis and Treatment. Buenos Aires, Argentina. July 2001.

Walsh JC, Hertogs K, Gazzard BG. Viral drug resistance, adherence and pharmacokinetic indices in HIV-1 infected patients on successful and failing protease inhibitor (PI) based highly active antiretroviral therapy (HAART). [Abstract] 40th ICAAC. September 2000

Andrea N. James, MD
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8/2/04

Concurrence
HFD-530/DivDirector/DBirnkrant
HFD-530/MO TL/RJohann-Liang

Cc: sNDA 20-977
sNDA 20-978
HFD-530/DepDivDir/Jmurray
HFD-530/PharmToxRev/Wu
HFD-530/PharmToxTL/Farrelly
HFD-530/ChemRev/Kambhampati
HFD-530/ChemTL/Miller
HFD-530/MircroRev/Mishra
HFD-530/MicroTL/O'Rear

Clinical Review Section

HFD-530/PKRev/Zheng
HFD-530/PKTL/Reynolds
HFD-530/StatsRev/Smith
HFD-530/StatsTL/Soon
HFD-530/CPMS/Behr
HFD-530/CPMS/DeCicco
HFD-530/PM/TSinha

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/s/

Andrea James
8/2/04 12:25:08 PM
MEDICAL OFFICER

Rosemary Johann-Liang
8/2/04 04:04:05 PM
MEDICAL OFFICER

Debra Birnkrant
8/2/04 04:15:02 PM
MEDICAL OFFICER

TEAM LEADER MEMORANDUM

DATE:	July 27, 2004
TO:	Division File for sNDA 20-977 SE2/SO12 Division File for sNDA 20-978 SE2/SO14 Division File for NDA 21,652 Division File for NDA 20-977 SLR-013 Division File for NDA 20-987 SLR-015
FROM:	Rosemary Johann-Liang, M.D. Medical Team Leader. Division of Antiviral Drug Products HFD-530
DRUG and INDICATION:	ZIAGEN™ (abacavir sulfate) Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection (addition of once daily regimen) EPZICOM™ (abacavir sulfate and lamivudine) Fixed Dose Combination Tablet, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection.
APPLICANT:	GlaxoSmithKline

This memorandum includes a brief overview and team leader concurrence for regulatory approval of the following applications that have been reviewed by DAVDP.

A. Supplemental NDAs 20-977 and 20-978: ZIAGEN® dosing of 600 mg PO QD (concurrences on primary clinical reviews by Andrea James, MD and Ozlem Belen, MD)

B. NDA 21, 652: ZIAGEN 600 mg and EPIVIR 300 mg PO QD in fixed-dose combination tablet (concurrences on primary clinical reviews by Andrea James, MD and Ozlem Belen, MD)

C. Labeling Supplement of ZIAGEN® to organize and update abacavir hypersensitivity reaction (ABC – HSR) information in the package insert, patient package insert, medguide, and warning card. (concurrences on primary clinical review by Andrea James, MD and Consumer Safety Officer Review by Tanima Sinha, M.S.)

A. Supplemental NDAs 20-977 and 20-978: ZIAGEN® dosing of 600 mg PO QD

Supplemental NDAs 20-977 (tablet) and 20-978 (oral solution) are applications for an already marketed nucleoside analog ZIAGEN® (abacavir sulfate). The applicant is seeking an alternative once daily dosing regimen (600 mg PO QD) in addition to the currently approved dose of 300 mg PO BID. In these sNDAs, the applicant has provided evidence via one well-controlled clinical study that ZIAGEN dosed 600 mg QD showed similar antiviral effect (assessed at 48 weeks duration) as compared to the standard dose of 300 mg BID when used in combination with other antiretroviral drugs for the treatment of HIV-1 infected, *antiretroviral-naïve* subjects. I concur with the clinical review prepared by Dr. Andrea James with assistance by Dr. Ozlem Belen. As stated in Dr. James' review, the applicant (GlaxoSmithKline) has demonstrated that ZIAGEN®, at the proposed doses for marketing, is a safe and effective drug for the treatment of HIV-1 infection in adults when combined with other antiretrovirals.

Briefly, the pivotal study that provided evidence for approval was study CNA30021 which was a phase III, 1:1 randomized, double-blind multicenter international study of 770 antiretroviral naïve subjects. The two arms of the study were abacavir (ABC) 600 mg QD + lamivudine (3TC) 300 mg QD + efavirenz (EFV) 600 mg QD versus abacavir 300 mg BID + lamivudine 300 mg QD + efavirenz 600 mg QD. The primary efficacy endpoint was the proportion of subjects with HIV-1 viral load < 50 copies/mL through week 48 analyzed using DAVDP's time to loss of virologic response (TLOVR) algorithm. The final efficacy outcome resulting from analysis by Dr. James and by Dr. Frazer Smith (DAVDP's statistical reviewer) are as follows.

Outcomes of Randomized Treatment Through Week 48 (CNA30021)

Outcome	ZIAGEN 600 mg q.d. plus EPIVIR plus Efavirenz (n = 384)	ZIAGEN 300 mg b.i.d. plus EPIVIR plus Efavirenz (n = 386)
Responder*	64% (71%)	65% (72%)
Virologic failure†	11% (5%)	11% (5%)
Discontinued due to adverse reactions	13%	11%
Discontinued due to other reasons‡	11%	13%

*Patients achieved and maintained confirmed HIV-1 RNA <50 copies/mL (<400 copies/mL) through week 48 (Roche® AMPLICOR Ultrasensitive HIV-1 MONITOR standard test version 1.0).
†Includes viral rebound, failure to achieve confirmed <50 copies/mL (<400 copies/mL) by Week 48, and insufficient viral load response.
‡Includes consent withdrawn, lost to follow up, protocol violations, clinical progression, and other.

After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 188 cells/mm^3 in the group receiving abacavir 600 mg once daily and 200 cells/mm^3 in the group receiving abacavir 300 mg twice daily. Through Week 48, 6 subjects (2%) in the group receiving ZIAGEN 600 mg once daily (4 CDC classification C events and 2 deaths) and 10 subject (3%) in the group receiving ZIAGEN 300 mg twice daily (7 CDC classification C events and 3 deaths) experienced clinical disease progression.

Treatment-emergent clinical adverse reactions (rated by the investigator as at least moderate) with a ≥5% frequency during therapy with ZIAGEN 600 mg once daily or ZIAGEN 300 mg twice daily both in combination with lamivudine 300 mg once daily and efavirenz 600 mg once daily

from Study CNA30021 were similar (for hypersensitivity reactions the ZIAGEN once daily arm showed a rate of 9% in comparison to ZIAGEN twice daily arm of 7%). However, compared to patients receiving ZIAGEN 300 mg twice daily, the incidence of *severe drug hypersensitivity* reactions was *higher* in patients who received ZIAGEN 600 mg once daily. Five percent (5%) of the ZIAGEN 600 mg once daily patients had severe drug hypersensitivity reactions compared to 2% of the ZIAGEN 300 mg twice daily treatment group. In the patients experiencing ABC-HSR, 4/36 (11%) experienced hypotension in the once daily group versus none in the twice daily group.

Clinical Signs and Symptoms Associated with ABC-HSR: Accent on the *severity* difference

	ABC OAD (N=384)	ABD BID (N=386)
	N=36 ABC-HSR cases	N= 28 ABC-HSR cases
HSR Symptoms Reported	n (%)	n (%)
Any rash	29/36 (81%)	20/28 (71%)
Disseminated rash	28/29 (97%)	17/20 (85%)
Localized rash	61/29 (3%)	3/20 (15%)
Maximum rash grade:		
1 & 2	12 (75%)	18 (90%)
3 & 4	7 (25%)	2 (10%)
Tachycardia	7/36 (19%)	2/28 (7%)
Hypotension	4/36 (11%)	0

Specific Important Issues

(Solutions to resolve these issues are in italics following each issue)

1. **Once daily dosing PK parameters:** Supportive PK studies for these supplemental applications were Study CAL 10001 and STUDY CNA 10905. These studies provided human pharmacokinetic information on plasma ZIAGEN concentrations at the new dosing regimen proposed (600 mg once daily) as well as intracellular carbavir phosphate (CBV-TP) concentrations following a steady state of ZIAGEN at the 300 mg twice daily regimen. The sponsor has not yet provided CBV-TP concentrations following the administration of ZIAGEN 600 mg once daily. This additional information may provide useful information in determining whether or not drug levels are maintained in the once daily dosing. Virological data and the development of resistance can then be assessed in the context of a thorough understanding of ZIAGEN's pharmacokinetic parameters.

- *This issue has been addressed with the appliant and the applicant has committed to providing this human PK information on ZIAGEN given 600 mg once daily (see below under Phase IV commitments).*

2. **Once daily dosing experience in treatment-experienced patients:** All of the ZIAGEN regulatory approvals in the adult HIV-1 population have been with data from antiretroviral treatment-naïve patients including the current CNA30021. Virology data in treatment experienced patients (those with baseline mutations being treated with ZIAGEN) are needed to characterize the resistance profile of ZIAGEN. Although in study CNA30021 the virologic failure rates were 11% for both arms, the prevalence of M184V/I substitution was higher in on-therapy isolates from the once daily (53%) virologic failure group with genotype data available than that in the BID (40%) group. The statistical significance of this

observation could not be established because of the low number of subjects with genotype data available at the time of virologic failure. However, further exploration of the relationship between ZIAGEN drug levels when given once daily and possibly increased resistance development is needed. In particular, this important question should be addressed in the antiretroviral treatment-experienced population where clinical as well as virology data are currently lacking with the once daily dosing regimen.

- *This issue has been addressed with the applicant and the applicant has committed to providing the clinical and virological data on ZIAGEN given 600 mg once daily versus 300 mg twice daily in an antiretroviral-experienced population (see below under Phase IV commitments)*

3. **Increased incidence of severe ABC-HSR with once daily dosing:** Study CNA30021 showed that there is an increased incidence of severe ABC-HSR when ZIAGEN is dosed 600 mg OAD as compared to 300 mg BID. The severe ABC-HSR included tachycardia and hypotension in the OAD group.

- *Because this is an extremely important safety concern and applies directly to the usage choice of the product, an additional usage statement will be placed under the INDICATIONS and USAGE section of the package insert.*

Applicant's Phase IV commitments for sNDAs 20-977 and 20-978: ZIAGEN® dosing of 600 mg PO once daily

Additional post-marketing commitment: Pediatrics

B. NDA 21,652: ZIAGEN 600 mg and EPIVIR 300 mg PO QD in fixed-dose combination (FDC) tablet

Supplemental NDA 21, 652 is an application for a fixed dose combination of the antiretroviral drugs abacavir sulfate 600 mg and lamivudine 300 mg, both of which are approved individually under the brand names of ZIAGEN™ and EPIVIR™, respectively.

This FDC product is being approved based on a large well-controlled clinical study (CNA30021, **please reference the previous section A for efficacy and safety overview)** which showed that ZIAGEN dosed once daily had similar antiviral effect as ZIAGEN dosed twice daily both in conjunction with EPIVIR and efavirenz. The benefit that this fixed-dose combination (FDC) will provide to patients is decreased pill burden as this FDC is administered as one pill once daily. Currently, ZIAGEN can be administered as two pills once daily or one pill twice daily. EPIVIR can be administered as one pill once or twice daily. I concur with the clinical review prepared by Dr. Andrea James with the assistance of Dr. Ozlem Belen recommending the regulatory approval of this FDC to be taken once daily as a safe and effective alternative regimen when combined with other antiretrovirals.

Specific Safety Concern regarding the use of this FDC (EPZICOM™)
(Solutions to resolve these issues are in italics following each issue)

1. **Increased incidence of severe ABC-HSR with once daily dosing:** First, this FDC contains the once daily 600 mg dose of ZIAGEN. Consequently, the safety concern of more severe ABC-HSR with the once daily discussed under the ZIAGEN OAD application applies here as well. The solutions are also similarly applicable and are as follows. (Please also see the Office of Drug Safety's consultation on this important safety topic)

- *Because this is an extremely important safety concern and applies directly to the usage choice of the product, an additional usage statement will be placed under the INDICATIONS and USAGE section of the package insert.*

- *Further, the sponsor has also committed to submitting another study (ESS101822) which will address the increased HSR severity issue as a Phase IV commitment (see below).*

2. **Third product with ABC-HSR:** Secondly, this FDC when introduced onto the marketplace will be the third medicinal product that will contain abacavir sulfate, the moiety that causes ABC-HSR. ZIAGEN and TRIZIVIR are the other two products already available. There have been no overt major safety consequences from the introduction of the second abacavir-containing product (TRIZIVIR) on to the market place. However, since the utmost importance in the safe use of abacavir containing products has to do with inadvertent "re-challenge" concern, strong educational programs and safe-guards need to be in place as the third product containing abacavir is introduced into the market.

- *The following safety information (with appropriate rewording for different sections of the label) will be highlighted throughout the FDC product package insert, patient package insert, the patient Medguide, and patient Warning card. "Previous clinical trials showed that there is a possibility of this hypersensitivity reaction occurring in approximately 8% of the patients. EZICOM should be discontinued a soon as a hypersensitivity reaction is suspected. EZICOM or other abacavir-containing products must not be restarted following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death"*

Specific Efficacy Concerns regarding the use of this FDC (EPZICOM™)
(Solutions to resolve these issues are in italics following each issue)

3. **Triple Nucleoside Antiretroviral Regimens:** The 2003 Department of Human and Health Services guidelines have relegated the triple nucleoside regimen, Trizivir, to the position of "alternative regimen" to be used only if a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) based regimens cannot be used or tolerated. This came in the wake of a growing mound of experience showing that triple nucleoside regimens are inferior in their ability to virologically suppress and maintain suppression as compared to NNRTI and PI based regimens. The following are two recent studies from the literature that illustrates this efficacy concern. For both studies, virologic non-response was defined as a failure to achieve a 2 log drop from baseline by week 8 or a 1 log increase above nadir on any subsequent visit.

Study name and Design	Arm One # and % virologic non-response	Arm Two # and % virologic non-response	Genotype Data	Consequence
ESS30009 Phase III, randomized, open-labeled study	ABC/3TC Fixed-dose combination + TDF 30/63 (47.6%)	ABC/3TC Fixed-dose combination + EFV 3/62 (4.8%)	In the triple FDC+TDF arm, 13 failures with M184V and 23 failures with M184V + K65R	Study was terminated prematurely
Farthing et al Small pilot study to assess efficacy of ABC/3TC FDC + TDF in naïve subjects	N=20 subjects enrolled; 9/17 (52%) had viral load rebound	-----	M184V mutation alone in n=5; M184V + K65R mutations in 4 subjects; 2 wildtype	Study was prematurely interrupted

Both of the studies above used the ABC/3TC fixed-dose combination, which is dosed once daily. Concerns about once daily regimen in regards to resistance development (please see previous section) are applicable here. Thus, this FDC product should be used as a component of a regimen containing NNRTI or PIs at the current time for optimal activity. Triple nucleoside/tide therapy regimen which includes EZICOM is not recommended.

4. **Lack of once daily dosing experience in antiretroviral-experienced population:** Another efficacy concern is the lack of virological data in the antiretroviral treatment-experience population. This issue was discussed in the previous section as follows. All of the ZIAGEN regulatory approvals in the adult HIV-1 population have been with data from antiretroviral treatment-naïve patients including the current CNA30021. Virology data in treatment experienced patients (those with baseline mutations being treated with ZIAGEN) are needed to characterize the resistance profile of ZIAGEN. Although in study CNA30021 the virologic failure rates were 11% for both arms, the prevalence of M184V/I substitution was higher in on-therapy isolates from the once daily (53%) virologic failure group with genotype data available than that in the BID (40%) group. The statistical significance of this observation could not be established because of the low number of subjects with genotypic data available at the time of virologic failure. However, further exploration is warranted of the relationship between ZIAGEN drug levels when given once daily with possibly increased resistance development. In particular, this important question should be addressed in the antiretroviral treatment-experienced population where clinical as well as virology data are currently lacking with the once daily dosing regimen.

WITHHOLD 2 PAGE(S)

C. NDA 20-977 (SLR-013) and NDA 20-978 (SLR-015): Labeling supplements to update the ABC-HSR safety information to the traditional ZIAGEN® PI, PPI, Medguide, Warning Card

Background: The original NDAs were submitted on June 24, 1998 and Ziagen® received accelerated approval on December 17, 1998. The traditional approval was April 15, 2004. In order to update and facilitate the multiple ZIAGEN-related regulatory applications under review (see previous sections A and B), the applicant submitted these labeling supplements to revise ABC-HSR related text in the Box WARNING, WARNINGS, CONTRAINDICATIONS, and PRECAUTIONS: Information for Patients and ADVERSE REACTIONS sections of the package insert. Additionally, the applicant made HSR related text revisions in the Medication Guide and Warning card. These updates are a full response to the first Phase IV commitment outlined in the traditional approval letter issued April 15, 2004 for ZIAGEN®.

Purpose: Theses supplements propose to improve consistency of HSR information across multiple sections of the professional prescribing information, Medication Guide and Warning Card; update HSR information to reflect the most recent data collected in clinical trails; Improve readability and understandability for the prescriber/healthcare provider and the patient; and eliminate unnecessary redundancy, where possible.

Review:

Professional Labeling

The black box warning was updated to reflect changes in the Hypersensitivity Reactions (HSR) warnings. An additional statement was added to the INDICATIONS AND USAGE section to bring attention to HSRs and to avoid reintroduction of abacavir sulfate to a patient with a history of hypersensitivity to abacavir sulfate. An additional statement was added to the CONTRAINDICATIONS section to bring attention to HSRs and to avoid reintroduction of abacavir sulfate to a patient with a history of hypersensitivity to abacavir sulfate. The WARNINGS sections were reworded and reorganized to bring attention to HSRs and the signs and symptoms associated with hypersensitivity reactions. Also added was a figure illustrating the frequency of hypersensitivity-related symptoms as reported in clinical trials.
Also provided are changes to the Clinical Management of Hypersensitivity under the WARNINGS sections to make it more concise. An, Information for Patients section was added in the professional labeling, specifically, information that should be conveyed to the patients by the healthcare provider.

Dr. James reviewed the supportive materials for HSR submitted with the traditional approval sNDAs 20-977/20-978. She determined that prospective data from nine clinical trials (n = 2670) report an average HSR rate of 8% rather than the rate of 5% that is currently in the label. The nine trials included in the HSR analysis were APV30001, APV30002, APV30003, CNA30024, ESS40001, ESS40002, ESS40003, ESS40006, and ESS40009. Figure 1 in the new proposed label utilizes data from these nine clinical trials to report the signs and symptoms most commonly associated with HSR. This HSR rate of 8% is consistent with the data from the two large pivotal clinical trials (CNAB3005 and CNA30024) submitted in support of ABC traditional approval and also with the two arms (9%, 7%) of the most recent study (CNA30021) reviewed for the ZIAGEN once daily and FDC products. The original 5% rate comes from a larger database of clinical

trials; however, these trials lack uniformity in how HSR was defined (for example respiratory signs/symptoms were not included initially) and how HSR data were collected. The concern is that the more restrictive HSR definition and the variable collection methods may bias in favor of a lower rate of HSR. Based on the above, DAVDP has revised the label to reflect the more conservative rate of HSR at 8%.

Medication Guide and Warning Card
The medication guide and warning card were both updated with more concise information regarding hypersensitivity reactions to abacavir sulfate. Also included are information on how to recognize signs and symptom of HSR and the effects of reintroduction of abacavir sulfate to patients with a history of hypersensitivity to abacavir sulfate.

DAVDP reviewers worked in conjunction with the Office of Drug Safety reviewers to update the Medication Guide and Warning Card to be more compatible with patient's reading emphasis and comprehension.

This updated ABC – HSR revisions to the traditional ZIAGEN label, PPI, Medguide and Warning Card will be incorporated to the ZIAGEN once daily, new FDC product, and TRIZIVIR labels, PPI, Medguide and Warning Cards so that same consistent message regarding this important safety information will be disseminated.

Concurrence
HFD-530/DivDirector/DBirnkrant

Cc: NDA 20-977 and NDA 20-978
HFD-530/DepDivDir/JMurray
HFD-530/MO/AJames
HFD-530/PM/TSinha

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

/s/

Rosemary Johann-Liang
8/2/04 03:54:12 PM
MEDICAL OFFICER

Revised TLMemo: Please sign off. Thanks.

Debra Birnkrant
8/2/04 04:04:07 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	DUE DATE 8/3/04	1. ORGANIZATION HFD-530	2. NDA NUMBER 20-977

3. NAME AND ADDRESS OF APPLICANT
SmithKline Beecham Corporation d/b/a Glaxo SmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

4. TYPE OF SUPPLEMENT
PA

5. DOCUMENT(S)

NUMBER	DATED	RECEIVED
SE2-012	10/2/03	10/3/03

6. NAME OF DRUG
Ziagen®

7. NONPROPRIETARY NAME
Abacavir sulfate (USAN)

8. SUPPLEMENT PROVIDES FOR: once-daily dosing for Ziagen (abacavir sulfate) tablets for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults.

9. AMENDMENTS/DATES

10. PHARMACOLOGICAL CATEGORY
Antiviral

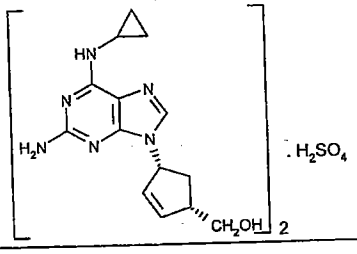
11. HOW DISPENSED
|X| •• || OTC

12. RELATED IND/NDA/DMF(s)
NDA 20-978
NDA 21-205
IND #45,331 (abacavir sulfate tablets and oral solution)

13. DOSAGE FORM(S)
Tablet

14. POTENCY (CIES)
300 mg of abacavir as abacavir sulfate/tablet

15. CHEMICAL NAME AND STRUCTURE
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)



16. MEMORANDA

17. COMMENTS
This is a Prior Approval sNDA for seeking approval of once-daily dosing (two 300 mg tablets) for Ziagen (abacavir sulfate) Tablets, 300 mg, for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults. The applicant did not propose any changes to the currently approved chemistry, manufacturing, and controls (CMC) for Ziagen tablets. The applicant requested for an exemption from the environmental assessment requirement as according to 21 CFR Part 25.31(a) because the action on this NDA does not increase the use of the active moiety. The following labeling changes were proposed in the Package Insert and Medication Guide and they were accepted by the Applicant.

Package Insert: Description
ZIAGEN Tablets are for oral administration. Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.
ZIAGEN Oral Solution is for oral administration. ~~One~~ Each milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (i.e., 20 mg/mL) as active ingredient ~~in an aqueous solution~~ and the following 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, and water.

Medication Guide:

What are the ingredients in Ziagen?

~~**Active ingredient:** abacavir sulfate~~

~~**Inactive ingredients:**~~ **Tablets: Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir as active ingredient and the following inactive ingredients:** ~~Each Ziagen Tablet contains~~ colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film-coating is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

Oral Solution: ~~One~~ Each milliliter (1 mL) of Ziagen Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (i.e, 20 mg/mL) as active ingredient ~~in an aqueous solution~~ and the following 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, and water.

In conclusion, the applicant will incorporate the proposed PI and Medication Guide changes in the next printed versions and this sNDA is recommended for approval.

18. CONCLUSIONS AND RECOMMENDATIONS

The supplement #SE2-012 to the NDA #20-977 is recommended for approval.

19. REVIEWER

NAME	SIGNATURE	DATE OF DRAFT REVIEW
Rao V. Kambhampati, Ph.D. Senior Regulatory Review Scientist	*[signed electronically in DFS]*	7/24/04

20. CONCURRENCE: HFD-530/TL/SMiller *[signed electronically in DFS]*

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/s/

Rao Kambhampati
7/28/04 05:09:01 PM
CHEMIST
Recommended for approval.
Please sign of and file.

Stephen Paul Miller
7/29/04 05:51:53 PM
CHEMIST

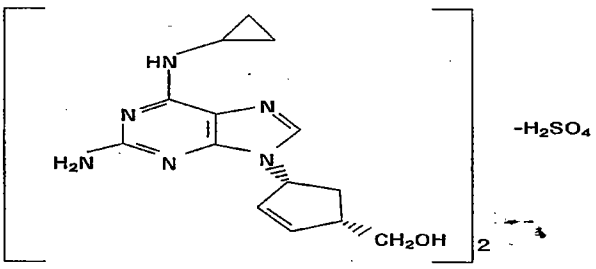
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

PHARMACOLOGY REVIEW

PHARMACOLOGIST'S REVIEW

NDA NUMBER:	**20977**
NUMBER/DATE/TYPE:	S012/Jan-2004
VOL #	1 volume
INFORMATION TO SPONSOR	Yes () No (x)
SPONSOR	GlaxoSmithKline, Research Triangle Park, North Carolina 27709
DRUG MANUFACTURER	Same as above
REVIEWER NAME:	Kuei-Meng Wu
DIVISION NAME:	DAVDP
HFD #:	HFD-530
REVIEW COMPLETION	2/8/04
DRUG TRADE NAME:	Ziagen™
GENERIC NAME	Abacavir sulfate
CODE NAME	Abacavir sulfate (1592U89 sulfate)
CHEMICAL NAME	*(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1) (enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring)
FORMULA/MW	$C_{14}H_{18}N_{50}\bullet H_2SO_4$; MW: 670.76
STRUCTURE	
RELEVANT NDAS	NDA 20-978 Abacavir Oral Solution
RELEVANT INDS	
DRUG CLASS:	Antiviral
INDICATION:	Treatment of HIV infection
CLINICAL FORMULATION:	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 hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.
ROUTE	Oral

DISCLAIMER: Tabular and graphical information is from sponsor's submission unless stated otherwise.

COMMENTS	This is once-a-day dosing supplement of abacavir Tablet (NDA 20-977). The NDA received an accelerated approval on 12/17/98. All preclinical information is cross-referenced to the original NDA. No additional pharm/tox information is included in this supplement and no changes in the pharmacology/toxicology section of the drug label are intended (please see EDR files at \\CDSESUB1\N20977\S_012\2004-0302). No regulatory comments on pharm/tox are needed, except the following editings/rewrites on labeling changes proposed by the sponsor are provided.
REGULATORY CONCLUSION	Pharm/tox portion of the labeling is commented (added text underlined) as below:

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Abacavir was administered orally at 3 dosage levels to separate groups of mice ~~(60 females and 60 males per group)~~ and rats ~~(56 females and 56 males in each group)~~ in two-year carcinogenicity studies. ~~Single doses were 55, 110, and 330 mg/kg/day in mice and 30, 120, and 600 mg/kg/day in rats.~~ Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose ~~(300 mg twice daily)~~. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

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,~~ ~~a~~Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

Abacavir ~~was not mutagenic~~ tested negative 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~~ a dose ~~of up to 500 mg/kg/day, a dose expected to produce exposures~~ approximately 8 times ~~fold higher than that in humans~~ the human exposure at the recommended ~~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.

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.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP
Concurrences:
HFD-530/PTL/JFarrelly
Wu/Pharm/2/4/04
Disk: HFD-530/PTL/JFarrelly

HFD-530/JFarrelly

cc:
HFD-530 NDA S_012
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HFD-530/CSO/
HFD-530/MO/
HFD-530/Pharm/
HFN-340

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/s/

Kuei Meng Wu
7/21/04 03:40:06 PM
PHARMACOLOGIST

James Farrelly
7/22/04 10:19:39 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
sNDA 20, 977/SE2-012; sNDA 20, 978/SE2-014
Reviewer: LALJI MISHRA, Ph.D. **Review Completed: 07/08/04**

Date Submitted: 10/02/03
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Sponsor: GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709
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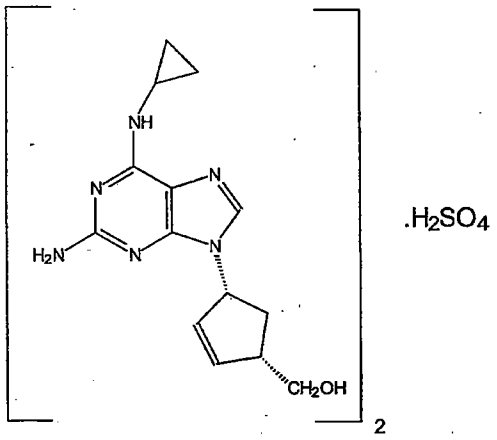
Product Names:

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

Structure



ABACAVIR

Indication: Treatment of HIV-1 infection in combination with other antiretroviral drugs
Route of Administration/Dosage Form: Oral/Tablet

Additional submissions reviewed:

Supplement #	Date of Correspondence	Date of Receipt
N20977/ SE2-012/BI	03/02/04	03/05/04
N20977/SE2-012/BI	06/14/04	06/18/04
N20977/SE2-012/BI	06/16/04	06/22/04
N20977/SE2-012/BI	06/17/04	06/22/04
N20977/SE2-012/BP	06/25/04	06/28/04
N20977/SE2-012/BZ	06/25/04	06/28/04
N20977/SE2-012/BI	06/30/04	06/30/04

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
sNDA 20, 977/SE2-012; sNDA 20, 978/SE2-014
Reviewer: LALJI MISHRA, Ph.D. **Review Completed: 07/08/04**

N20977/SE2-012/BI	07/06/04	07/08/04
N20977/SE2-012	07/08/04	07/08/04
N20977/SE2-012/BL	07/14/04	07/14/04

BACKGROUND

GlaxoSmithKline (GSK) Inc. has filed supplemental new drug applications (sNDAs) # 20-977 SE2-012 & 20-978 SE2-014 to provide results from clinical studies in support of once-daily (OAD) dosing of abacavir (ABC) for the treatment of HIV-1 infection, and seeks marketing approval for Ziagen Tablets and Ziagen Oral Solution. ABC first received accelerated approval on December 17, 1998 and traditional approval on April 15, 2004. ABC is a synthetic carbocyclic nucleoside analogue that inhibits HIV-1 reverse transcriptase (RT) activity, and is a member of the nucleoside reverse transcriptase inhibitor (NRTI) class. The (+) enantiomer of abacavir sulfate, in contrast to the (-) enantiomer, lacks anti-HIV-1 activity, and was inactive at a concentration of 200 μM (Daluge et al., 1997). In most of the virologic preclinical studies, abacavir is referred to as 1592U89.

In the current application, GSK has submitted the results of the pivotal clinical trial CNA30021 to support efficacy and safety of OAD dosing of abacavir in antiretroviral naïve HIV-1 infected patients. In addition, GSK has submitted results from a pharmacokinetic study, CNA 10905 in support of OAD dosing of abacavir.

Data on the metabolism and mechanism of action of abacavir, in vitro anti-HIV-1 activity of abacavir, cytotoxicity, in vitro combination activity relationships of abacavir with approved antiretroviral agents, selection and characterization of abacavir resistant HIV-1 in vitro and in vivo, and cross-resistance with other NRTIs were previously reviewed (microbiology reviews of original NDA # 20-977 and original NDA # 20-978 dated November 25, 1998, and sNDA # 20-977 SE7-011/sNDA # 20-978 SE7-013, dated June 6, 2000) and briefly summarized earlier (microbiology review of sNDA 20-977 SE7-011 and sNDA 20-978 SE7-013 dated March 10, 2004). A summary of the metabolism, mechanism of action of abacavir (ABC) and ABC drug resistance is reproduced here. In addition, the sponsor recently submitted in vitro antiviral activity data against non-B clades and updated in vitro combination activity of ABC/3TC to include recently approved antiretroviral agents, and data on the susceptibility of abacavir resistant clinical HIV-1 isolates to approved NRTIs, NNRTIs and PIs and effects of abacavir-resistance associated mutations on in vitro susceptibility to NRTI and NNRTIs.

ABC is phosphorylated intracellularly to its 5'-monophosphate by the cellular enzyme adenosine phosphotransferase. Subsequently, ABC monophosphate is deaminated to carbovir monophosphate (CBV-MP) by a cytosolic deaminase. CBV-MP is then further converted to di- and triphosphate forms by cellular kinases (Faletto et al., 1997) forming the guanosine triphosphate analogue CBV-TP, the active moiety of ABC. The

intracellular half-life of CBV-TP was 3.3 hours in dividing CEM cells (Faletto, 1994, Daluge et al., 1997).

CBV-TP inhibits the activity of HIV-1 RT both by competing with the natural substrate, deoxyguanosine 5'-triphosphate (dGTP), and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated CBV-MP prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA synthesis is terminated.

HIV-1 isolates with reduced susceptibility to ABC have been selected in vitro and were also obtained from patients treated with ABC (Tisdale and Cousens, 1994; Tisdale et al., 1997). Genotypic analysis of ABC resistant isolates selected in vitro and clinical isolates from patients failing an ABC-containing regimen showed mutations in the RT gene that resulted in the K65R, L74V, Y115F, and M184V amino acid substitutions. Mutations M184V and L74V were most frequently observed in clinical isolates.

The in vitro phenotypic susceptibility to ABC of recombinant viruses containing either single, double, or triple ABC resistance-associated mutations was evaluated (Tisdale et al., 1997). This study showed that recombinant viruses containing a single ABC-resistance-associated amino acid substitution (K65R, L74V, Y115F, or M184V) exhibited 2- to 4-fold reduced susceptibility to ABC compared to wild-type HIV-1_{HXB2}. Similarly, recombinant viruses containing double substitutions associated with ABC-resistance without M184V (K65R + L74V, L74V + Y115F) exhibited 3- to 4-fold reduced susceptibility to ABC compared to wild type HIV-1_{HXB2}. However, recombinant viruses with double ABC resistance-associated substitutions containing M184V (K65R + M184V, L74V + M184V, Y115F + M184V) exhibited 7- to 9-fold reduced susceptibility to ABC compared to wild type HIV-1_{HXB2}. Additionally, recombinant viruses containing triple substitutions associated with ABC resistance (K65R/L74V/M184V or L74V/Y115F/M184V) exhibited 10- to 11-fold reduced susceptibility to ABC compared to wild type HIV-1_{HXB2} (Tisdale et al., 1997).

Cross-resistance of viruses containing ABC-resistance-associated mutations to other NRTIs was assessed. Recombinant viruses containing the K65R and L74V substitutions exhibited 3-fold reduced susceptibility to ddC and ddI, and 12-fold reduced susceptibility to 3TC compared to wild type HIV-1_{HXB2}. Similarly, recombinant viruses containing K65R and M184V substitutions exhibited 5- to 7-fold reduced susceptibility to ddC, ddI, and >70-fold reduced susceptibility to 3TC compared to wild type HIV-1_{HXB2}. Furthermore, recombinant viruses containing triple substitutions (K65R/L74V/M184V or L74V/Y115F/M184V) exhibited 5- to 6-fold reduced susceptibility to ddC, ddI, and a >70 fold reduced susceptibility to 3TC. Recombinant viruses containing the L74V substitution alone, or in combination with M184V, or in triple combination with Y115F and M184V (L74V/Y115F/M184V) exhibited 2- to 5- fold reduced susceptibility to ddC and ddI and a 2- to >70-fold reduced susceptibility to 3TC as compared to wild type HIV-1_{HXB2}(Tisdale et al., 1997).

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
sNDA 20, 977/SE2-012; sNDA 20, 978/SE2-014
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Data on the genotypic and phenotypic analyses of isolates from clinical studies CNA 30021 are reviewed here. Mitochondrial toxicity of ABC and relevant PK data are also summarized in this review. Additionally, data on the antiviral activity of ABC against HIV-1 isolates of different clades, HIV-2 isolates, in vitro combination activity of ABC/3TC with approved antiretroviral agents, effect of ribavirin on the antiviral activity of ABC, data on the susceptibility of abacavir resistant clinical HIV-1 isolates to approved NRTIs, NNRTIs and PIs and effects of abacavir resistance-associated mutations on in vitro susceptibility to NRTI and NNRTIs are also reviewed. For efficacy results of CNA30021, please see the reviews of the Medical Officer Andrea James, M.D. and Statistician Fraser Smith, Ph.D. For intracellular concentration of carbovir triphosphate and other PK parameters, please see the review of the Biopharmaceutical Reviewer, Jenny Zheng, Ph.D.

SUMMARY

Clinical study CNA30021:

Title: Analyses of HIV Genotypic and Phenotypic Data Collected during the Course of Clinical Study CNA30021: A Phase III, 48-week, Randomized, Double-blind, Multicenter Study to Evaluate the Safety and Efficacy of Abacavir (ABC) 600mg Once-daily (OAD) vs Abacavir 300mg BID in Combination with Lamivudine (3TC, 300mg OAD) and Efavirenz (EFV, 600mg OAD) in Antiretroviral Therapy Naïve HIV-1 Infected Subjects.

Objective: To assess the genotypes and phenotypes of HIV-1 isolates in antiretroviral naïve virologic failure subjects treated with ABC OAD versus ABC BID in combination with 3TC and EFV.

I. Subject Accountability:

A summary of the ITT-Exposed population and sub-study population sizes is provided in Table 1 (NDA 20-977/SE2-012, Vol 5, Page 34, Table 5).

Table 1: Subject Accountability

Population	ABC OAD	ABC BID	Total
All Subjects Randomized	392	392	784
ITT-E	384	386	770
Random sample	97	99	196
Virologic failure	44	44*	88
Virologic failure (Rebound)	15	17	32
Virologic failure (Non-response)	29	27	56

*For resistance analyses, patients # 51676, #52643, and #53385 who were not technically virologic failures but treatment failures were included.

Antiretroviral naïve subjects were randomized 1:1 to the ABC OAD (n=384) or BID (n=386) arms with a background regimen of 3TC OAD + EFV OAD.
A sub-population of 196 subjects (ABC OAD: n = 97, ABC BID: n = 99) was selected at random for baseline genotypic analysis. Genotypic and phenotypic analyses were performed for baseline and on-therapy isolates from most subjects with virologic failure.

Virologic failure was defined as 1) **Rebound**: confirmed (two consecutive) plasma HIV-1 RNA values ≥50 copies/mL after achieving a confirmed level <50 copies/mL during the treatment phase, 2) **Never Suppressed**: Plasma HIV-1 RNA levels never achieved confirmed suppression (<50 copies/mL) with at least 48 weeks of randomized treatment, or 3) **Insufficient Viral Response**: Plasma HIV-1 RNA levels never achieved confirmed suppression (<50 copies/mL) prior to week 48 and the investigator identified the reason for treatment discontinuation prior to week 48 due to insufficient plasma HIV-1 RNA response. The categories never suppressed and insufficient viral response were analyzed together in this report as the non-response group.

The Virologic Failure population (n=88) constituted 44 subjects from the OAD group and 44 subjects from the BID group. Subjects who discontinued prematurely due to insufficient virologic response were included with the never suppressed group of subjects in the non-response population. These subjects had never achieved RNA suppression to < 50 copies/mL.

II. Baseline Plasma HIV-1 RNA Strata for Analysis Populations

Baseline plasma HIV-1 RNA levels stratum for subjects in each treatment group is shown in Table 2. In the ITT-Exposed population, the number of subjects in both the treatment groups with a baseline plasma HIV-1 RNA stratum of either ≤ 100,000 or > 100,000 copies/mL were similar. Similarly, the number of subjects selected as a random sample from both these strata were similar in both treatment groups. However, more subjects in each treatment group with virologic failure had baseline RNA levels of >100, 000 copies/mL (OAD 26/44; BID 23/44. These virologic failure subjects included rebounders and non-responders (Table 2, NDA 20-977/SE2-012, Vol 5, Page 39, Table 8). Similarly, 18/44 virologic failure subjects in the OAD group and 19/44 subjects in the BID group with baseline RNA of ≤100,000 copies/mL were rebounders and non-reponders.

Table 2. Baseline Plasma HIV-1 RNA Strata for Analysis Population

Baseline Plasma HIV-1 RNA	ABC OAD N=384	ABC BID N=386	Total N=770
ITT-E			
≤ 100,000 copies/mL	217/384	217/386	434/770
> 100,000 copies/mL	167/384	169/386	336/770
Random Sample			
≤ 100,000 copies/mL	54/97	56/99	110/196

> 100,000 copies/mL	43/97	43/99	86/196
Virologic Failure : Rebound			
≤ 100,000 copies/mL	8/15	10/17	18/32
> 100,000 copies/mL	7/15	7/17	14/32
Virologic failure : Non-response			
≤ 100,000 copies/mL	10/29	9/27	19/56
> 100,000 copies/mL	19/29	18/27	37/56

III. Availability of genotypic data for the virologic failure subjects

Samples for genotypic and phenotypic resistance evaluation in the virologic failure population were analyzed at baseline and at the time of virologic failure. Random samples were genotyped at baseline only. The genotypic analysis was performed for samples with a plasma HIV-1 RNA >500 copies/mL. All genotypic analyses were carried out at GSK by trained scientific staff using the Phenotypic analysis was carried out by using the investigational single cycle

The availability of genotypic data from the virologic failure population is shown in Table 3 (NDA20-977/SE2-012, Vol 5, Page 41, Table 10 and electronic submission NDA 20-977/SE2-012/BI dated 06/08/04, and 07/08/04).

Table 3. Availability of genotypic data for the virologic failure subjects

Assessment	ABC OAD N=44	ABC BID N=44	Total N=88
Baseline	40	34	74
Post-baseline	18	20	38
No-GT[a]	26	24	50
Baseline and Post-baseline	18	20	38

[a]genotype not available (plasma HIV-1 RNA ≤ 500 copies/mL at or after time of virologic failure)

IV. Analysis of clades for HIV-1 isolates from random and virologic failure subjects

HIV-1 isolates from all subjects genotyped at baseline and post-baseline were analyzed for HIV-1 group and clade as indicated by the RT nucleotide sequence. All HIV-1 isolates were of group M. As expected, the majority of viruses were of clade B, and the distribution of clades was similar across the therapy groups in the random sample (Table 4, NDA20-977, Vol 5, Page 41, Table 11).

Table 4. Analysis of HIV-1 clade for isolates from random subjects

Clade	ABC OAD N=97	ABC BID N=99	Total N=196
B	90	93	183
Total Non-B	7	6	13
B/F	1	1	2
C or C/AC	5	3	8
F1	0	1	1
F1/BF	1	0	1
06-CPX	0	1	1

A similar analysis was undertaken for the population of subjects showing virologic failure (Table 5; NDA20-977/SE2-012, Vol 5, Page 42 and electronic submission NDA20-977/SE2-012/BZ, dated 06/25/04). The majority of the isolates from virologic failure subjects were classified as Clade B and the number of non-clade B isolates was low.

Table 5. Analysis of HIV-1 clade for isolates from virologic failure subjects

Clade	ABC OAD N=44*	ABC BID N=44*	Total N=88
B	42	37	79
Total Non-B	2	3	5
A/AD/AC	0	1	1
F1	0	1	1
F1/BF	0	1	1
F1/F2/BF	1	0	1
06-CPX/GK/02AG	1	0	1

*=clade data not available for 4 subjects in the BID group (# 51124, # 51676, # 52473, and # 52643).

V. Genotypes of baseline isolates from random subjects receiving ABC OAD + 3TC + EFV or ABC BID + 3TC + EFV

Table 6 (NDA 20-977/SE2-012, Vol 5, Pages 43-44, Tables 13-14) shows the genotypes of baseline isolates from random subjects enrolled in the ABC OAD or BID treatment groups.

Table 6. Genotypes of baseline isolates from random subjects in the ABC OAD and BID treatment groups

RT mutations	ABC OAD N=94	ABC BID N=98	Total N=192
NRTI-resistance-associated mutations			
M41L	1	0	1

E44D	0	1	1
D67N	1	0	1
V118I	2	2	4
M184V	1	0	1
L210W	0	1	1
K219Q/E	1	0	1
NNRTI resistance-associated mutations			
K103N	1	5	6
V179D	1	2	3
Y181C*	0	1	1

*present in combination with K103N

The baseline isolates from 7/94 subjects in the OAD group and 10/98 subjects in the BID group contained NRTI- and NNRTI-resistance-associated amino acid substitutions. The genotypes of baseline isolates from 3 subjects in the OAD group and 1 subject in the BID group were not available. In general, only one resistance-associated substitution was observed in isolates from an individual. The most common NRTI resistance-associated substitution was V118I, present in baseline isolates from 2 subjects in each treatment group. However, one subject in each treatment group with a V118I substitution in the baseline isolates was a responder. Similarly, one subject (# 53248) in the OAD group with the M184V substitution in baseline isolates was also a responder at week 48. One subject (# 51243) in the OAD group with the M41L substitution in baseline isolates discontinued after 24 weeks due to an adverse event. The most common NNRTI resistance-associated substitution at baseline was K103N (OAD: n=1, # 52578; BID: n=5, # 51421, # 51506, # 52911, # 51440, # 51490). The substitution K103N confers cross-resistance to all of the currently approved NNRTIs. Of the 6 subjects with viruses having a K103N mutation at baseline, 4 subjects were responders (HIV-1 RNA level <50 copies/mL) after 48 weeks of therapy. Two subjects in the BID group with baseline isolates containing K103N substitutions (# 51440 and # 52911) were non-responders after 48 weeks of therapy. The baseline isolates from subject # 52911 contained two substitutions, K103N and Y181C. This subject received therapy for only two weeks before discontinuing therapy for 'other' reasons and was lost to follow up after 24 weeks. The other subject (# 51440) with baseline isolates containing a K103N substitution who failed to respond to therapy, was lost to follow-up after 36 weeks. Both subjects were designated as non-responders for non-virologic reasons. The NNRTI substitution, V179D, was present in the baseline isolates from 1 subject (# 53142) in the OAD group, and in isolates from 2 subjects in the BID group (# 52959, # 52701). Subject # 52959 was a virologic failure. One subject (# 52701) in the BID group with V118I and V179D substitutions in baseline isolates discontinued prematurely after 48 weeks due to an adverse event. However, this patient was grouped as a virologic failure at week 48.

VI. Genotypes of baseline isolates from virologic failure subjects randomized to the ABC OAD and BID treatment groups

The genotypes of baseline isolates from 4/44 virologic failure subjects in the OAD group and 8/44 subjects in the BID group were not available (Table 3). The baseline isolates from 8/44 subjects in the OAD group and 4/44 subjects in the BID group contained NRTI and NNRTI resistance-associated substitutions (Table 7; NDA20-977/SE2-012, Vol 5 , Page 49, Table 18 and electronic submission NDA20-977/SE2-012/CRT, dated 10/02/03). Some of these substitutions were present in combination. The prevalence of NRTI and NNRTI resistance-associated substitutions in baseline isolates was higher (18%) in subjects randomized to the OAD group than those in subjects in the BID group (10%). Table 7 shows that one or more of the NRTI and NNRTI resistance-associated substitutions were present in baseline isolates of virologic failure subjects in both treatment groups. Most of the substitutions were present in isolates from non-responders except for the baseline isolates from 1 subject in each treatment group who under went virologic rebound.

Table 7. Genotypes of baseline isolates from virologic failure subjects randomized to the ABC OAD or BID treatment group

Substitutions	ABC OAD		ABC BID	
	Rebound N=15	Non-response N=29	Rebound N=17	Non-response N=27
M41L	0	1	0	1
K103N	0	1	0	0
V118I	0	1	1	0
V179D	0	1	1	1
Y188L	0	1	0	0
M41L, E44D, V118I	0	1	0	0
K70R, Y188L, K219Q	0	0	0	1
K103N, Y188C, G190A	1	0	0	0
M41L, V118I, M184V, T215Y, K219Q	0	1	0	0

VII. Genotypes of on-therapy isolates from virologic failure subjects receiving ABC OAD, or ABC BID

Genotypic data for on-therapy isolates were available from subjects with HIV-1 RNA >500 copies/mL or after the time of virologic failure up to 48 weeks of therapy. Tables 8 (NDA20-9777, Vol 5, Pages 50-51, Tables 19-20 and electronic submission 20-977/SE2-012/BI, dated 07/08/04), and 9 (NDA20-977/SE2-012, Vol 5, Pages 60-61, Table 25, and electronic submission 20/977/SE2-012, BI dated 07/08/04) show the prevalence and emergence of NRTI and NNRTI resistance-associated mutations in the on-therapy isolates from virologic failure subjects. More than one NRTI and/or NNRTI

resistance-associated mutations were present in on-therapy isolates from most virologic failure subjects.

Table 8. Summary of genotypes of on-therapy isolates from virologic failure subjects receiving ABC OAD, or ABC BID

RT mutations	ABC OAD N=44[a]	ABC BID N=44[a]	Total N=88
NRTI-resistance-associated substitutions			
M41L	2	1	3
K65R	1	0	1
K70R	0	1	1
L74V	5	3	8
Y115F	1	1	2
V118I	1	0	1
M184V/I	11	9	20
T215Y/F	1	1	2
K219Q/E	2	1	3
NNRTI resistance-associated substitutions			
L100I	2	0	2
K013N	8	11	19
V106I	1	0	1
V108I	1	0	1
V179D	3	1	
Y181C	0	2	2
Y188H/L/Y	2	2	4
G190S/A	2	1	3

[a]On-therapy genotype available from N=18 subjects in the ABC OAD and N=18 subjects in the ABC BID treatment groups

Genotypes were determined for 18 and 20 subjects in the OAD and BID arms, respectively. The genotypes of on-therapy isolates from 26 virologic failure subjects in the OAD group and 24 subjects in the BID group were not available due to technical (PCR) difficulties and/or recent classification as virologic failure. The genotypes of on-therapy isolates from 4 subjects in the OAD group and 6 subjects in the BID group were wild-type.

The main NRTI resistance-associated substitutions selected during therapy were M184V/I (OAD: n=10; BID: n=8) and L74V (OAD: n=5; BID: n=3). The L74V substitution was always present in combination with the M184V substitution. Isolates from 1 subject (# 52278) in the OAD group retained substitutions M41L, V118I, M184V, T215Y, K219Q present in baseline isolates and developed NNRTI resistance-associated substitutions during therapy (Table 9). Similarly, isolates from another subject (# 53750) in the OAD group maintained the M41L substitution observed in baseline isolates. The

isolates from another subject, #51194, in the OAD group maintained the baseline NNRTI substitutions K103N and G190A and developed the ABC resistance-associated substitutions K65R, L74V, Y115F and M184V during therapy. Isolates from another subject (# 51637) from the OAD group developed K103N, M184V and K219Q substitutions during therapy. Isolates from the subject # 53329 in the OAD group maintained the baseline NNRTI substitution K103N and developed an additional NNRTI substitution, L100I, during therapy. Similarly, isolates from subject # 52278 in the OAD group developed the L100I and K103N substitutions during therapy. The NNRTI substitution V108I developed in isolates from only one subject (# 52726) who was randomized to the OAD group. The on-therapy isolates from one subject (# 51660) from the BID group developed the mutations L74V, V106I, and M184V/I, and Y188L (NNRTI resistance-associated mutation) and maintained the K70R, Y188L and K219Q mutations observed in baseline isolates. Similarly, the on-therapy isolates from another subject (# 52661) also retained the baseline mutation M41L and developed the K103N, M184V and T215Y mutations during therapy. The on-therapy isolates from subject # 52278 in the OAD group maintained the M41L, V118I, M184V, T215Y, and K219Q mutations present in baseline isolates and selected the L74V, L100I and K103N mutations during therapy. The on-therapy isolates from subject # 51124 contained mutations M184I and K103N week 48 and wild type genotypes at baseline.

The main NNRTI resistance-associated mutation selected during therapy was K103N (OAD, n=6; BID, n=12). The other NNRTI-resistance-associated mutations Y188C/L/H were observed in the on-therapy isolates from 2 subjects in each treatment group. The mutations Y188H along with K103N and M184V/I developed in on-therapy isolates from subject # 52020 (OAD) during therapy. Similarly, the on-therapy isolates from another subject, # 51573 (OAD), maintained the baseline mutation Y188L and developed the additional NNRTI resistance-associated mutations V106I and V179D. In the BID group, the on-therapy isolates from one subject (# 52181) contained the treatment-emergent substitutions K103N and Y188H/Y/L. The NNRTI resistance-associated substitution Y181C developed in the on-therapy isolates from two subjects (# 51621 and # 52884) in the BID group. The mutations Y181C along with other NNRTI resistance-associated mutations K103N and P225H and the ABC resistance-associated mutations L74V, Y115F and M184V developed during therapy in the on-therapy isolates from subject # 51621. Similarly, the on-therapy isolates from another subject (# 52884) selected the L74V, Y181C, M184V and G190S mutations during therapy.

VIII. Phenotypic analysis of baseline and on-therapy isolates from virologic failure subjects

Phenotypic analysis was performed for baseline isolates from most virologic failure subjects (n=73). Phenotypic analysis of the on-therapy isolates was performed only for isolates from subjects with plasma HIV-1 RNA >500 copies/mL at the time of failure or later within 48-week window. Baseline isolates from 37/44 virologic failure subjects in the OAD group were susceptible to ddC, d4T, TDF and ZDV, and isolates from 40/44

subjects susceptible to ABC and 3TC. Similarly, baseline isolates from 38 subjects in the OAD group exhibited in vitro susceptibility to ddI. Baseline isolates from 29/44 subjects in the BID group were susceptible to ddC, ddI, d4T, and TDF, and isolates from 33/44 subjects to ABC, 3TC and 28/44 subjects to ZDV. Similarly, baseline isolates from 5/44 subjects in the OAD group showed reduced susceptibility (≥2.5-fold) to EFV and NVP, and isolates from 8/44 subjects to DLV. Similarly, isolates from 5/44, 3/44, and 4/44 subjects in the BID group showed reduced in vitro susceptibility to DLV, EFV, and NVP, respectively.

The baseline isolates harboring the amino acid substitutions K103N and M184V exhibited ≥2.5-fold reduced susceptibility to EFV and 3TC, respectively. Similarly, baseline isolates containing the V179D substitution (# 52253 and # 52958 in the OAD, and # 51094 and # 52959 in the BID groups) exhibited 2.8- to 3.5-fold reduced susceptibility to EFV in vitro.

Phenotypic data were available for 18 subjects in the OAD group and 17 subjects in the BID group (NDA 20-977, Vol 5, Table 8.44, Pages 298-299, and NDA 20977/SE2-012, dated 07/08/04). The cut off levels used by [redacted] for drug resistance were ≥ 4.5 FR (fold reduction in susceptibility) for ABC ≥ 2.5 FR for 3TC, and ≥ 2.5 FR for EFV.

Isolates from 13/18 and 8/17 virologic failure subjects in the OAD and BID groups, respectively, exhibited ≥2.5-fold reduced susceptibility to EFV in vitro. Similarly, isolates from 10/18 and 5/17 virologic failure subjects in the OAD and BID treatment groups, respectively, exhibited ≥2.5-fold reduced susceptibility to 3TC in vitro. As expected, isolates from 7/18 subjects in the OAD and 3/17 subjects in the BID group were resistant (≥2.5-fold reduced susceptibility) to ddC. Isolates from 3/18 and 2/17 virologic failure subjects in the OAD and BID treatment groups, respectively, exhibited ≥4.5-fold reduced susceptibility to ABC in vitro. The choice of a 4.5-fold shift for ABC resistance may not be appropriate given that the median fold changes in abacavir susceptibility were 1.5 (range 0.55 –11) and 0.83 (range 0.69-13) ~~for~~ isolates from virologic failure patients receiving ABC OAD and BID, respectively. As expected, ABC resistant isolates were cross-resistant to ddC and ddI. Similarly, EFV resistant isolates were cross-resistant to delavirdine and nevirapine.

IX. Relationship between on-therapy and treatment emergent resistance associated mutations and phenotype

The fold-increase in resistance (reduced drug susceptibility) in relation to treatment emergent resistance-associated amino acid substitutions is shown in Table 9. As expected, M184V and K103N are highly predictive of resistance to 3TC and EFV, respectively. The substitutions G190A, Y188L, and V108I in the OAD group (subjects # 51402, # 51573, and #52726) and K103N (subject # 51124) and Y181C with G190S in the BID group (subject # 52884) contributed to reduced susceptibility to EFV in vitro.

Reduced susceptibility to ABC was associated with multiple ABC resistance-associated substitutions, i.e., K65R, L74V, Y115F, M184V (subjects # 51194, # 52278, and # 53329 in the OAD group, and # 51621 and # 52884 in the BID group). Substitutions M184V and L74V in the context of multiple TAMs and/or with 2 or more NNRTI substitutions, (subjects # 52278 and # 53329), but not the M184V or M184I substitutions by themselves (subjects # 51285 and # 52958 in the OAD group), nor M184V/I with one or two NNRTI resistance-associated substitutions (subjects # 51000, # 51637, # 52020, and # 52726 in the OAD group and # 52170 in the BID group) reduced the in vitro susceptibility of on-therapy isolates to ABC.

Table 9. Treatment emergent resistance–associated substitutions and fold-resistance to study drugs

Subject Number	Therapy	Substitutions at virologic failure*	FR to ABC	FR to 3TC	FR to EFV
51000	OAD	**K103N, M184V, P225H**	2.1	>99	198
51194	OAD	**K65R, L74V,** K103N, **Y115F, M184V,** Y188C, G190A	11	>81	>217
51219	OAD	**K103N**	0.79	1.09	45
51260	OAD	**K103N**	0.55	1.09	34
51285	OAD	**M184I**	1.5	>103	0.74
51402	OAD	**L74V, M184V, G190A**	3.7	>81	>217
51550	OAD	**None**	1.03	1.08	1.34
51573	OAD	**L74V, M184V,** Y188L	3.8	>112	>231
51637	OAD	**K103N, M184V, K219E**	4.0	>81	46
52020	OAD	**K103N, M184V/I, Y188H**	1.1	95	>243
52278	OAD	M41L, **L74V, L100I, K103N,** V118I, M184V, T215Y, K219Q	5.8	>88	>235
52426	OAD	None	0.98	1.3	2.7
52726	OAD	**V108I, M184V**	0.86	1.2	36
52754	OAD	None	0.59	0.80	3.4
52761	OAD	**None**	0.84	0.91	2.08
52958	OAD	**M184V**	3.8	>116	1.5
53329	OAD	**L74V, L100I,** K103N, **M184V**	5.2	>102	>243
53750	OAD	M41L	0.82	0.79	0.92
51032	BID	None	-	-	-
51124	BID	**M184I, K103N**	3.48	>97	7.5
51220	BID	None	0.69	0.78	1.1
51413	BID	**K103N**	0.83	0.75	35

51621	BID	**L74V, K103N, Y115F, Y181C, M184V, P225H**	13	>116	>251
51660	BID	K70R, **L74V, V106I, M184V/I,** Y188L, K219Q	4.3	>94	>217
52170	BID	**K103N, M184V**	2.0	>75	128
52181	BID	**K103N, Y188F/H/Y/L**	0.68	1.1	200
52247	BID	**K103N**	-	-	-
52269	BID	**K103N**	0.83	0.73	16
52274	BID	None	0.85	0.96	0.83
52405	BID	None	0.77	0.87	0.62
52661	BID	M41L, **K103N, M184V, G190S**	-	-	-
52884	BID	**L74V, Y181C, M184V, G190S**	5.7	>81	>217
53131	BID	None	0.8	0.9	1.0
53136	BID	**K103N**	0.82	0.68	75
53385	BID	**K103N, M184V, Y188C**	-	-	-
51676	BID	**K103N**	1.05	1.18	34
52643	BID	**K103N, M184V**	3.48	>100	13
53753	BID	**None**	0.70	0.67	0.96

*Bold = mutations that emerged during therapy. Mutations in normal font were present at baseline.

Comment

On-therapy isolates from subject # 52726 in the OAD group developed the M184V substitution during therapy, but surprisingly exhibited no reduced susceptibility to 3TC in vitro.

X. Relationship between treatment–emergent resistance substitutions and virologic response

The median plasma HIV-1 RNA level at baseline and at the time of virologic failure for subjects with treatment emergent substitutions are shown in Table 10 (NDA 20-977/SE2-012, Vol 5, Page 65, Table 28 and electronic submission NDA20-977/SE2-012/CRT, dated 10/02/03). In the OAD group, subjects with treatment emergent substitutions (n=13) showed a reduction in the plasma HIV-1 RNA levels of 0.41 to 2.02 $\log_{10}$ copies/ml (n=12). However, the HIV-1 RNA of one subject with on-therapy isolates containing the L74V, L100I and K103N substitutions (subject # 52278) increased by 0.15 $\log_{10}$ copies at the time of virologic failure. Subjects in the OAD group failing therapy with wild type virus (subjects, # 51550, # 52426, # 52754, and # 52761), or no change in genotype from baseline (subject # 53750) showed a reduction of 0.45 $\log_{10}$ copies/mL at the time of virologic failure.

In the BID group, virologic failure subjects with the treatment emergent substitutions showed a median HIV-1 RNA reduction of 0.20 to 1.58 $\log_{10}$ copies/mL from baseline. Subjects failing with the K103N substitution alone (n=4: # 51413, # 52247, # 52269, and # 53135) showed an overall reduction of 0.42 $\log_{10}$ copies/mL. Virologic failure subjects with wild-type HIV-1 genotypes (# 51032, # 51220, # 52274, # 52405, # 53131, and # 53753) showed a reduction of 0.44 $\log_{10}$ copies/mL at the time of virologic failure.

At the time of virologic failure, subjects in both the OAD and BID treatment groups with no genotype available had a reduction of HIV-1 RNA levels of 3.48 to 3.66 $\log_{10}$ copies/mL from baseline.

Table 10. Relationship between treatment emergent substitutions and virologic response

ABC OAD + 3TC + EFV (n=44)			
Substitution(s)	**Median $\log_{10}$ plasma HIV-1 RNA at baseline**	**Median $\log_{10}$ plasma HIV-1 RNA at failure**	**Median $\log_{10}$ change from baseline**
No genotype (n=26)	5.18	1.70	-3.48
Wild-type (n=4) # 51550, 52426, 52754, 52761, (or as baseline # 53750)	4.67	4.22	-0.45
K103N (n=2) # 51219, 51260	5.16	4.87	-1.07
M184V/I (n=2) # 51285, 52958	5.09	3.46	-1.63
L74V, M184V (n=2) #51402, 51573	5.70	3.69	-2.02
V018I, M184V (# 52726)	5.48	4.26	-1.22
L74V, L100I, K103N (# 52278)	5.18	5.32	0.15
L74V, L100I, M184V (# 53329)	5.20	4.79	-0.41
K103N, M184V/I, Y188H (# 52020)	4.53	3.58	-0.95
K103N, M184V, K219E (# 51637)	5.14	3.91	-1.23
K103N, M184V, P225H (# 51000)	5.29	4.46	-0.83
K65R, L74V, Y115F, M184V (# 51194)	4.66	3.73	-0.93
ABC BID + 3TC + EFV (N=44)			
No genotype (n=24)	5.52	1.86	-3.66
Wild–type (n=6) # 51032, 51220, 52274, 52405, 53131, 53753	4.74	4.30	-0.44
K103N (n=4) # 51413, 52247, 52269, 53136	4.49	3.93	-0.42
L74V, M184V/I (# 51660)	4.80	3.22	-1.58
K103N, M184V (# 52170, # 51124, # 53385)	5.03	3.26	-1.77

K103N, Y188F/H/L (# 52181)	4.49	3.90	-0.58
L74V, Y181C, M184V (# 52884)	6.11	5.61	-0.50
K103N, M184V, T215Y (# 52661)	4.95	3.91	-1.04
L74V, K103N, Y115F, Y181C, M184V, P225H (# 51621)	5.59	5.40	-0.20

XI. Other Pre-clinical and Pharmacokinetic (PK) studies pertinent to the current NDA

XI (a). Effect of CBV-TP on cellular DNA polymerase γ in vitro and mitochondrial toxicity

The effect of CBV-TP on human cellular DNA plymerases was previously reviewed (please see microbiology review of NDA 20977/SE7-011, March 10, 2004). Cellular DNA polymerase γ is involved in the synthesis of mitochondrial DNA. The effect of CBV-TP on the activities of cellular DNA polymerase γ was investigated. Based on the K_i/K_m ratio (Table 11; microbiology review of NDA 20977/SE7-011, March 10, 2004) it appears that CBV-TP does not inhibit DNA polymerases γ. In contrast to CBV-TP, ddGTP is a strong inhibitor of DNA polymerase γ.

Table 11. K_i values for CBV-TP and ddGTP (Source: Reardon, 1994, GSK research report: TEZZ/94/007-00)

Enzyme	Inhibitor	K_i (μM)	K_i/K_m
Pol γ	CBV-TP	14 ± 2	100
	ddGTP	0.016 ± 0.002	0.12

The K_m values for dGTP for cellular polymerase γ was: = 0.14 ± 0.01 μM.

In another study, Lee et al., 2003 examined the mitochondrial toxicity of CBV-TP by measuring the rates of incorporation of CBV-TP, and its rates of removal by the DNA polymerase and exonuclease activities associated with the mitochondrial DNA polymerase γ, respectively. These authors calculated the toxicity index for most of the FDA approved NRTIs. The calculation of toxicity index was based upon the hypothesis that the primary cause of the toxicity results from inhibition of mitochondrial DNA replication, and is computed to represent the relative increase in time required to replicate the mitochondrial genome based upon the probability of incorporation of each drug and the times it takes for the proof reading exonuclease to remove it after incorporation. The toxicity index values (fractional increase in time required to replicate the mitochondrial genome) for ABC, ddC, ddI , stavudine (d4T), 3TC, tenofovir (TFV), and ZDV were: 0.03, 9000, 6.8, 2000, 0.40, 1.5, and 0.20. Thus, ABC, had the lowest and ddC the highest mitochondrial toxicity. CBV-TP had a very low toxicity index of 0.03. This implied that there would be a 3% increase in the time required to replicate the mitochondrial genome if the concentration of CBV-TP inside the mitochondria was equal to the concentration of dGTP.

XI (b). PK studies

Previous PK studies showed that in humans, the ABC $C_{max.ss}$ achieved was 10 μM (3.0 μg/mL) and the AUC_{τ} was 6.02 μg.h/mL at the therapeutic dose of 300 mg BID (original NDA 20-977 Vol l, Page 137). However, results from a recent PK study (CNA 10905) showed that the ABC $C_{max.ss}$ achieved with a 300mg BID dose was 3.0 μM (0.88 μg/mL). These PK data suggest that the C_{max} of ABC achieved with a BID dose would be very close to the IC_{50} values of the laboratory strains of HIV-1. This raises concerns about the serum concentration and antiviral activity in vivo of ABC OAD. The PK data for ABC OAD dosing are not available.

XI (c). Intracellular CBV-TP levels in patients taking ABC OAD

The objective of this study was to measure the intracellular levels of CBV-TP in HIV-1 positive patients taking ABC 600 mg OAD. Five HIV-positive adults taking ABC 600 mg OAD for 5-17 months as a component of multiple drug rescue therapy including two or three other nucleosides, one non-nucleoside, and one or two protease inhibitors participated in this pharmacokinetic study. Blood samples were drawn into cell preparation tubes (Vacutainer, CPT, Becton Dickinson, Franklin Lakes, NJ, USA) at time 0, (24 h after the previous ABC dose) and 1, 12, 14-16, 18, 20, 22, and 24 hr after an observed 600 mg ABC dose. PBMCs were isolated and phosphates extracted using 60% methanol. The methanol extracts were then dried and stored at -70^{0}C. After a second extraction with perchloric acid, endogenous dGTP levels were determined by a DNA polymerase assay. For the measurement of CBV-TP, reaction mixtures included ^{3}H-dGTP, template-primer and RT in a total volume of 50 μL. Radioactivity bound to the primer was separated by spotting onto filter papers and washing, and was then determined by liquid scintillation counting. CBV-TP and dGTP concentrations are shown in Table 12 (Harris et al., 2002)

Table 12. CBV-TP and dGTP concentrations in PBMCs of patients treated with 600 mg ABC OAD

Time (h)	CBV-TP fmoles/10^6 cells median (range)	dGTP fmoles/10^6 cells median (range)	N Samples
0	211 (127-575)	49 (26-73)	5
1	196 (107-670)	59 (18-171)	4
12	188	104	1
14-16	267 (101-548)	54 (14-111)	6
18	176 (113-648)	52 (22-83)	5
20	158 (80-660)	60 (29-94)	4
22	107 (105-201)	52 (42-82)	3
24	184 (62-354)	49 (34-75)	5

In this study, except for one patient, intracellular CBV-TP levels greater than 100 fmoles/10^6 cells (greater than 200 nM) were sustained over the entire 24 h period after a single 600 mg ABC dose. The half-life of CBV-TP was estimated to be greater than 12 h. These investigators suggested that since the intracellular level of CBV-TP (>200 nM) achieved with a 600 mg ABC OAD is about 10 times the concentration of K_i (21 nM) of CBV-TP for HIV-1 RT, once a day dosing of ABC is supported. However, the K_i value reported was obtained from an in vitro reaction using purified HIV-1 RT and a calf thymus DNA as a template-primer (Daluge et al., 1997). Additional pharmacokinetic studies with 600 mg ABC OAD may be needed (please refer to the review of Dr. Jenny Zheng, PK reviewer for this NDA).

XII. Antiviral activity of ABC against a panel of HIV-1 isolates representing clades A, B, C, D, E, F, G, and HIV-2 (GSK report RH2004/0089/00)

The purpose of this study was to determine the anti-HIV-1 activity of ABC against a panel of twenty-four HIV-1 isolates representing clades A, B, C, D, E, F, G (HIV-1 group M), three isolates from HIV-1 group O and 3 HIV-2 isolates. All virus isolates were obtained from NIH AIDS Research and Reference Reagent Program. PHA-stimulated PBMCs were plated in a 96 well round bottom microplate at a concentration of 5 x 10^4 cells/well. Each plate contained virus/cell control wells (cell plus virus), experimental wells (drug plus cells plus virus), and compound control wells (drug plus media without cells). Test drug concentrations were prepared at a 2X concentration in microtiter tubes and 100 µL of each concentration was placed in appropriate well using the standard format. Fifty µL of a HIV-1 stock was placed in each test well (m.o.i.= 0.1). The PBMC cultures were maintained at 37^0C (5% CO_2) for 7 days following infection. After 7 days, cell-free supernatant samples were collected and RT activity determined using a microtiter plate-based RT assay as described (Buckheit et al., 1991). For the determination of cell viability and cytotoxicity, 20 µL tetrazolim–based dye MTS (Cell Titer 96 Reagent, Promega) was added per well. The microtiter plates were then incubated 4-6 hrs at 37^0 C. Plates were read spectrophotometrically at 490/650 nm with a Molecular Devices Vmax or SpectraMaxPlus plate reader. The anti-HIV-1 activity of ABC against HIV-1 isolates from different clades are shown in Table 13 (NDA20-9777/SE2-012, electronic submission, GSK report RH2004/0089/00, Pages 9-11, Table1).

Table 13. Anti-HIV-1 activity of ABC against isolates form different clades

HIV-1 Isolate	Subtype	IC_{50}(nM)	TC_{50} (nM)	TI TC_{50}/IC_{50}
RW/92/009	A	14.8	>10,000.0	>676
UG/92/029	A	676.0	>10,000.0	>14.8
UG/92/037	A	344.3	>10,000.0	>29
Br/92/014	B	1056.9	>10,000.0	>9.46
Jr-CSF	B	27.9	>10,000.0	>358.4

TH/92/026	B	5.86	>10,000.0	>1706.5
Br/92/025	C	16.7	>10,000.0	>598.8
IN/93/101	C	1.47	>10,000.0	>6802.7
MW/93/959	C	8.09	>10,000.0	>1236.1
UG/92/001	D	35.7	>10,000.0	>280.1
UG/92/024	D	396.3	>10,000.0	>25.2
UG/92/046	D	356.5	>10,000.0	>28.1
CMU 06	E	105.3	>10,000.0	>95.0
CMU 08	E	168.4	>10,000.0	>59.4
TH/93/073	E	28.1	>10,000.0	>355.9
BR/93/029	F	47.6	>10,000.0	>210.1
BR/93/019	F	5.19	>10,000.0	>1926.8
BR/93/020	F	199.7	>10,000.0	>50.1
G3	G	7.07	>10,000.0	>1414.4
JV1083	G	176.6	>10,000.0	>56.6
RU132	G	51.4	>10,000.0	>194.6
BCF01	O	22.4	>10,000.0	>446.4
BCF02	O	281.9	>10,000.0	>35.5
BCF03	O	598.3	>10,000.0	>16.7

Table 13 shows that the average IC_{50} value of ABC against HIV-1 isolates representing different clades was 0.193 ± 0.267 μM (range=0.0015-1.05 μM). These values are in agreement with the IC_{50} value of ABC reported for clinical isolates (0.26 ± 0.18 μM) Table 14 (electronic submission NDA20-9777/SE2-012/BI, dated 06/16/04, GSK report RH2004/0089/00, Pages 11-12, Table 2) shows that the IC_{50} value of ABC against HIV-2 isolates ranged from 0.024 to 0.49 μM. Abacavir exhibited similar antiviral activity against HIV-1 and HIV-2 isolates. The overall assay performances were validated by the positive control compound ZDV, which exhibited the expected levels of antiviral activity in each of the assays (electronic submission NDA20-9777/SE2-012/BI, dated 06/16/04, GSK report RH2004/0089/00, Pages 11-12, Table 2).

Table 14. Anti-viral activity of ABC against HIV-2 isolates

HIV-2 Isolate	IC_{50} (nM)	TC_{50} (nM)	TI TC_{50}/IC_{50}
CDC 310319	171.0	>10,000	>58.5
CDC 310342	23.7	>10,000	>421.9
CBL-20	489.6	>10,000	>20.4

XIII. Effect of ribavirin (RBV) on the anti-HIV-1 activity of ABC (GSK research report RH2004/00092/00)

The objective of this study was to determine the effect of RBV on the antiviral activity of ABC in MT4 cells. The in vitro combination antiviral activity was determined by a checkerboard style experimental design as described earlier. In these experiments, drug A was always RBV and drug B was ABC. Dilutions were arranged so that every concentration of each drug was tested in the presence and absence of every concentration of the other. Aliquots of ABC were serially diluted vertically in a deep-well master assay plate in RPMI 1640 medium containing 10% FBS at concentrations that were 40-fold higher than the final assay concentration. RBV was diluted horizontally across a separate master plate in RPMI 1640 containing 10 % FBS at concentration that were 40-fold higher than the final assay concentration. Test concentration range for ABC was 25 μM to 25 nM and for RBV 50 μM to 50 nM. Anti-HIV-1 activity assays were performed in triplicate for each combination and direct cytotoxicity test as a single read out for each combination. MT-4 cells were infected and treated with drugs as described before. After 5 days of incubation, the infected cells were treated with 20 μL of Cell titer 96 MTS reagent and processed as described before. The OD was measured at 492 nM using a microplate absorabance reader. IC_{50} values were calculated as described earlier. The IC_{50} value of RBV was >40 μM (electronic submission, NDA20-977/SE2-012/BI, dated 06/14/04, GSK Document Number RH 2004/00015/00). The IC_{50} values of ABC in the absence and presence of 50 μM RBV were 15.5 and 15 μM, respectively (GSK report RH2004/00092/00, Page 19, Table 1). Results from this study confirmed previous findings that RBV has no effect on the anti-HIV-1 activity of ABC.

XIV. Resistance and cross-resistance of ABC to NRTIs, NNRTIs and PIs

Title: Resistance and cross-resistance analyses of clinical isolates relevant to abacavir plus lamivudine combination therapy (GSK research report RH 2004/00088/00)

Objectives:

1. To evaluate the activity of ABC or 3TC against HIV-1 isolates resistant to approved NRTI, NNRTIs and PIs.
2. To evaluate the activity of antiretroviral agents (NRTIs, and NNRTIs) against HIV-1 isolates containing ABC/3TC-resistance-associated mutations (K65R, L74V, Y115F, and M184V/I).

Data base analyses were performed at
Phenotypic data for the samples were generated at
CA by published methods (Petropoulos et al., 2000). The data are presented as the fold change (FC) in the drug concentration that inhibits virus production by 50% (IC_{50}). The FC is the ratio of the IC_{50} value for the patient virus over the IC_{50} value for the wild type reference virus NL4-3, i.e., (IC_{50} value patient virus)/(IC_{50} value wild type virus). Resistance cutoffs are biologically or clinically defined. The biological cutoff is currently defined for the

Clinical cutoffs are based on clinical trial results, and represent the FC which is considered clinically significant.

XIV (a). Effects of ABC/3TC resistance associated mutations on ABC and 3TC resistance phenotype

The effects of ABC/3TC resistance-associated amino acid substitutions on ABC and 3TC resistance phenotypes are shown in Table 15 (electronic submission, NDA20-977/SE2-012/BI, dated 06/16/04, GSK research report RH 2004/00088/00, Page 15, Table 1). Data presented in Table 15 show that no single ABC-resistance-associated substitution alone caused resistance to ABC when the fold change cutoff value used to define ABC resistance phenotype was 4.5. However, it should be noted that the median fold shift in susceptibility to ABC for virus from patients failing ABC OAD was 1.3. The K65R or L74V substitutions in combination with the M184V substitution caused 5.6 to 6.9 median fold increase in resistance to ABC. This finding is in agreement with results obtained from in vitro studies summarized in the background section of this sNDA review. Table15 also shows that except for the L74V substitution, other substitutions, namely K65R alone or in combination with M184V, and M184V/I substitutions alone caused a median FC of 9.3- to 200-fold increase in 3TC resistance. Isolates with the L74V substitution alone were susceptible to 3TC (MFC=1.4). No sample with a Y115F substitution was present in this database.

Table 15. Effects of ABC/3TC resistance associated substitutions on ABC and 3TC resistance phenotype

ABC/3TC substitution	[1]Number of samples with		ABC (cutoff: 4.5)		3TC (cutoff:3.5)	
	[2]ZDV	TFV	median	min-max	median	min-max
K65R alone	82	80	2.5	1.3-5.3	9.3	3.2-22.9
K65R + M184V	54	54	6.9	3.5-11.4	200	200-200
L74V alone	22	22	1.6	0.7-2.3	1.4	0.5-2.5
L74V + M184V	74	68	5.4	2.9-8.5	200	200-200
Y115F alone	0	0	na	na	na	na
M184V alone	1720	1521	2.8	0.9-11.7	200	12.6-200
M184V alone	27	27	1.6	0.9-2.5	200	67.7-200

1= number of samples with data available for the indicated drug..

2= The number under ZDV equals the total number of samples for a given query.

na= not applicable

XIV (b). Effects of TAMS alone, or TAMs plus M184V on ABC resistance

Table 16 (electronic submission, NDA20-977/SE2-012/BI, dated 06/16/04, GSK research report RH 2004/00088/00, Page 15, Table 1) shows that combinations of TAMs (1 to 4 TAMs) did not confer resistance to ABC. On the other hand, some combinations of TAMs in the presence of the M184V substitution conferred resistance to ABC (M41L + L210W + T215F/Y, M41L + T215F/Y, D67N + K70R + T215F/Y + K219Q). However, a combination of certain TAMs failed to confer resistance to ABC even in the presence of the substitution M184V, i.e., D67N + K70R, or D67N + K70R + K219Q.

Table 16. Effects of TAMS alone, or TAMs plus M184V on ABC resistance

Thymidine analogue mutations	[1]number of samples with		ABC (cutoff=4.5)	
	[2]ZDV	TFV	median	min-max
T215F/Y-M184V	94	86	1.7	0.8-2.5
T215F/Y + M184V	114	100	4.4	1.8-7.8
D67N, K70R, -M184V	19	19	1.1	0.7-1.6
D67N, K70R, + M184V	30	18	3.4	2-5.5
M41L, L210W, T215F/Y-M184V	101	101	2.9	1-6.4
M41L, L210W, T215F/Y + M184V	204	181	6.1	2.5-9.2
M41L, T215F/Y-M184V	106	92	2.0	0.9-6.2
M41L, T215F/Y + M184V	269	245	4.5	2.8.7
D67N, K70R, K219Q-M184V	83	71	1.8	0.7-6.6
D67N, K70R, K219Q + M184V	181	158	3.8	2.3-6.7
D67N, K70R, T215F/Y, K219Q-M184V	50	45	2.4	1.2-5.6
D67N, K70R, T215F/Y, K219Q + M184V	72	67	5.3	2.9-8.8

1= number of samples with data available for the indicated drug..

2= The number under ZDV equals the total number of samples for a given query.

XIV (c). Effect of NNRTI resistance-associated mutations on ABC and 3TC resistance

Table 17 (electronic submission, NDA20-977/SE2-012/BI, dated 06/16/04, GSK research report RH 2004/00088/00, Page 16, Table 2) shows the effect of NNRTI resistance-associated substitutions on ABC phenotype. These results showed that none of the NNRTI mutation tested conferred phenotypic resistance to ABC or 3TC.

Table 17. Effect of NNRTI-resistance associated mutations on ABC and 3TC resistance

Mutations	ABC (cutoff: 4.5)		3TC (cutoff: 3.5)	
	median	min-max	med	min-max
K103N only (n=656)	0.8	0.4-1.4	0.9	0.4-2.6
G190S/A only (n=52)	0.9	0.5-1.4	0.9	0.6-2.1
Y181C/I only (n=55)	0.9	0.4-1.7	1.0	0.4-3.5
Y188L only (n=38)	1.0	0.5-1.4	1.1	0.5-2.3

All of the above NNRTI substitutions conferred resistance to EFV and NVP. The median FC ranged from 2.8 to 216 for EFV and 61 to 400 for NVP.

XIV (d). Effect of PI resistance-associated substitutions on ABC and 3TC resistance

PI substitutions, D30N, M46I/L, I50V, I54L/M, V82A/F/T/S, I84V and L90M were tested for their ability to confer resistance to ABC, or 3TC. The median FC values for ABC and 3TC ranged from 0.8 to 1.0 for HIV-1 isolates containing each of the above PI substitutions. These PI substitutions did not affect the in vitro susceptibility of isolates to ABC, or 3TC. However, these PI mutations conferred resistance to PIs tested (APV, IDV, NFV, and SQV).

XIV (e). Effect of ABC/3TC- resistance associated mutations on ZDV and d4T resistance

Table 18. Effect of ABC/3TC resistance associated mutations on ZDV and d4T resistance phenotypes

ABC/3TC mutations	[1]number of samples with		ZDV (cutoff=1.9)		d4T (cutoff=1.7)	
	ZDV	TFV	median	min-max	median	min-max
K65R alone	82	80	0.5	0.2-3.3	1.3	0.7-2.7
K65R + M184V	54	54	0.4	0.2-1.2	1.0	0.6-1.4
L74V alone	22	22	0.3	0.2-0.6	0.9	0.5-1.2
L74V + M184V	74	68	0.3	0.1-0.8	0.8	0.5-1.4
Y115F alone	0	0	na	na	na	na
M184V alone	1720	1521	0.4	0.1-2	0.7	0.4-2.1
M184I alone	27	27	0.2	0.1-0.4	0.8	0.5-1

[1]= number of sample with data available for the indicated drug
na= not applicable

Table 18 (electronic submission, NDA20-977/SE2-012/BI, dated 06/16/04, GSK research report RH 2004/00088/00, Page 19, Table 5) shows that isolates containing ABC resistance-associated mutations alone or in combination were susceptible to ZDV with the median FCs ranging from 0.3 to 0.6. HIV-1 isolates containing ABC/3TC resistance associated mutations were also susceptible to d4T. Isolates which did not contain K65R, but other ABC/3TC mutations were more susceptible to d4T.

XIV (f). Effect of ABC/3TC resistance-associated mutations on ddI and ddC resistance phenotype

Table 19. Effect of ABC/3TC resistance associated mutations on ddI and ddC resistance phenotype

ABC/3TC mutations	[1]number of samples with		ddI (cutoff=1.7)		ddC (cutoff=1.7)	
	ZDV	TFV	med	min-max	med	min-max
K65R alone	82	80	1.7	1.1-3.1	2.3	1.3-3.5
K65R + M184V	54	54	2.9	1.6-4.9	3.9	2.3-5.7
L74V alone	22	22	1.2	0.9-1.8	1.2	0.7-1.9
L74V + M184V	74	68	2.2	1.3-5	2.3	1.1-4.6
Y115F alone	0	0	na	na	na	na
M184V alone	1720	1521	1.4	0.7-5.9	1.6	0.7-12.8
M184I alone	27	27	1.4	1-2	2.0	1-2.8

[1]= number of sample with data available for the indicated drug
na= not applicable

Table 19 (electronic submission, NDA20-977/SE2-012/BI, dated 06/16/04, GSK research report RH 2004/00088/00, Page 20, Table 6) shows that the ABC resistance-associated mutations, K65R, K65R + M184V, and L74V + M814V conferred resistance to ddI and ddC. However, the median FC value for L74V, or M184V/I mutations were below the ddI resistance cutoff value of 1.7, suggesting that these mutation alone did not confer resistance to ddI. This result is surprising since the mutation L74V is known to confer ddI resistance. The median FC values for the L74V mutation was below ddC resistance

cutoff value of 1.7 suggesting that mutation L74V alone did not confer resistance to ddC. However, the mutation M184I alone conferred resistance to ddC.

XIV (g). Effect of ABC/3TC resistance–associated mutation on TFV resistance phenotypes

Table.20. Effect of ABC/3TC resistance–associated mutation on TFV resistance phenotypes

ABC/3TC mutations	[1]number of samples with		TFV (cutoff=1.4)	
	ZDV	TFV	median	min-max
K65R alone	82	80	1.8	0.8-4.2
K65R + M184V	54	54	1.1	0.7-2.2
L74V alone	22	22	0.5	0.4-0.6
L74V + M184V	74	68	0.3	0.2-0.6
Y115F alone	0	0	na	na
M184V alone	1720	1521	0.5	0.2-1.1
M184I alone	27	27	0.4	0.4-0.5

[1]= number of sample with data available for the indicated drug
na= not applicable

Table 20 (electronic submission, NDA20-977/SE2-012/BI, dated 06/16/04, GSK research report RH 2004/00088/00, Page 21, Table 7) shows that except for the K65R mutation, all other ABC-resistance associated mutations did not confer resistance to TFV. The mutation M184V increased the susceptibility of K65R containing isolates to TFV. The median FC of K65R + M184V containing isolates was 1.1, below the TFV resistance cut-off FC of 1.4. Isolates containing ABC-resistance associated mutations, L74V alone, L74V + M184V, M184V alone, or M184I were all susceptible to TFV (median FC ranged from 0.3 to 0.5).

XIV (g). Effect of ABC/3TC resistance associated mutations on NNRTI resistance phenotypes

Table 21. Effect of ABC/3TC resistance associated mutations on NNRTI resistance phenotypes

Mutation	DLV (cutoff=2.5)			EFV (cutoff=2.5)			NVP (cutoff=2.5)		
	n	med	min-max	n	med	min-max	n	med	min-max
K65R only	26	0.5	0.1-3.4	26	0.4	0.2-2.3	26	0.4	0.1-3.5
L74V only	4	0.9	0.4-3.4	4	0.8	0.3-2.4	4	0.8	0.3-1.7
M184V only	1346	0.9	0.1-250	1402	0.6	0.1-152	1397	0.7	0.1-168
K65R + M184V	65	0.5	0.1-15	65	0.4	0.2-1.9	65	0.4	0.1-13.6
L74V + M184V	18	0.7	0.3-1.5	18	0.5	0.2-1	18	0.5	0.2-1.3

Table 21 (electronic submission, NDA20-977/SE2-012/BI, dated 06/16/04, GSK research report RH 2004/00088/00, Page 22, Table 8) shows that none of the ABC-resistance-associated mutations alone, K65R + M184V or L74V + M184V mutations in combination decreased the susceptibility of isolates to the NNRTIs tested (DLV, EFV, and NVP).

CONCLUSIONS

With respect to microbiology, NDA # 20-977 and NDA # 20-978 are supported. In study CNA 30021, antiretroviral naïve subjects received either ABC OAD (n=384) or BID (n=386) in a background regimen of 3TC + EFV OAD. In support of OAD dosing of abacavir, the sponsor provided genotypic and phenotypic analyses data on baseline and on-therapy isolates from virologic failure subjects enrolled in study 30021. Forty-four subjects in the OAD group and 44 subjects in the BID group met the protocol defined virologic failure (plasma HIV-1 RNA level >50 copies/mL). The baseline isolates from 8/44 subjects in the OAD group and 4/44 subjects in the BID group contained NRTI and/or NNRTI resistance-associated mutations either alone or in combination. The prevalence of NRTI and NNRTI resistance-associated substitutions in baseline isolates was higher in subjects randomized to the OAD group (18%) than those from subjects in the BID group (10%). Genotypes of on-therapy isolates were available from 18/44 subjects in the OAD and 20/44 subjects in the BID group. The major NRTI resistance-associated amino acid substitutions selected during therapy were M184V/I (OAD: n=10; BID: n=8) and L74V (OAD: n=5; BID: n=3). The substitution L74V was always present in combination with the M184V substitution. The major NNRTI resistance-associated substitution selected during therapy was K103N (OAD: n=6; BID: n=12). In addition, on therapy isolates from virologic failure subjects contained one or more ABC-resistance-associated substitutions (K65R and Y115F), thymidine analogue substitutions (M41L, K70R, L210W, T215Y, K219Q/E) and NNRTI resistance-associated substitutions (L100I, V108I, V179D, Y181C, Y188H/L/Y, G190A/S, P225H).

The prevalence of M184V/I substitution was higher in on-therapy isolates from the OAD group than that in the BID group. The statistical significance of this observation could not be established because of the low number of subjects with genotypic data available at the time of virologic failure (OAD, n=18; BID, n=20). However, one plausible explanation for a high number of M184V/I mutations in on-therapy isolates from subjects receiving ABC OAD could be that the plasma levels of ABC in these subjects were sub-optimal. This explanation would be consistent with the small shifts in susceptibility found in the on therapy isolates from failure patients (median shift = 1.3). Data on the plasma levels of ABC in subjects receiving ABC OAD were not available. Virologic failure subjects with isolates containing the M184V/I mutation in both the treatment groups had a median HIV-1 RNA level of 3.91 $\log_{10}$ copies/mL at the time of virologic failure. Thus, HIV-1 replication was not suppressed in subjects with isolates containing the M184V/I mutation. However, other mutations in concert with the M184V/I might have contributed to virologic failure.

The baseline isolates harboring the substitutions K103N and M184V exhibited reduced susceptibility in vitro to EFV and 3TC, respectively. Similarly, baseline isolates containing the V179D substitution in the OAD and BID treatment groups exhibited 2.8- to 3.5-fold reduced susceptibility to EFV in vitro. Phenotypic analysis data for on-therapy isolates were available for 18 subjects in the OAD group and 17 subjects in the BID group. The isolates from the 13/18 and 8/17 failure subjects in the OAD and BID treatment groups, respectively, exhibited reduced susceptibility to EFV in vitro. Similarly, on-therapy isolates from the 10/18 and 5/17 failure subjects in the OAD and BID treatment groups, respectively, exhibited reduced susceptibility to 3TC in vitro. The on-therapy isolates from the 3/18 and 2/17 failure subjects in the OAD and BID treatment groups, respectively, exhibited reduced susceptibility to ABC in vitro. The phenotypes of baseline and on-therapy isolates correlated with genotypes.

In support of this sNDA, GSK recently submitted additional data on preclinical studies and resistance and cross-resistance studies on clinical isolates. The anti-HIV-1 activity of ABC against a panel of twenty-four HIV-1 isolates representing clades A, B, C, D, E, F, G (HIV-1 group M), three isolates from HIV-1 group O and 3 HIV-2 isolates was determined in PBMCs. The average IC_{50} value of ABC against HIV-1 isolates representing different clades was 0.193 ± 0.267 μM (range=0.0015-1.1 μM). These values are in agreement with the IC_{50} value of ABC reported for clinical isolates (0.26 ± 0.18 μM). The IC_{50} values of ABC against HIV-2 isolates ranged from 0.022 to 0.6 μM.

RBV has no effect on the anti-HIV-1 activity of ABC. The IC_{50} value of ABC in the absence and presence of 50 μM RBV was 15.5 and 15 μM, respectively

HIV-1 isolates containing ABC resistance-associated amino acid substitutions singly or in combination were tested for susceptibility to ABC or 3TC. Results showed that no single ABC resistance-associated substitution conferred resistance to ABC. However, the

substitution K65R or L74V in the presence of the M184V substitution conferred resistance to ABC (5.6- to 6.9-fold increase in the IC_{50} value). This finding is in agreement with results obtained from in vitro studies reviewed in the original NDA (NDA 20-977) and briefly summarized in the background section of this review. Except for the L74V substitution, other substitutions, namely K65R alone or in combination with M184V, and M184V/I substitutions alone caused a median FC of 9.3 to 200 in 3TC resistance. Isolates with the L74V substitution alone were susceptible to 3TC.

TAMs alone or combination of TAMs (1 to 4 TAMs) did not confer resistance to ABC. On the other hand, some combination of TAMs (M41L + L210W + T215F/Y, M41L + T215F/Y, D67N + K70R + T215F/Y + K219Q) in the presence of M184V conferred resistance to ABC.

None of the NNRTI resistance-associated substitutions (K103N, Y181C, Y188L, G190S/A) tested conferred phenotypic resistance to ABC or 3TC. Similarly, PI resistance–associated substitutions D30N, M46I/L, I50V, I54L/M, V82A/F/T/S, I84V and L90M were tested for their ability to confer resistance to ABC or 3TC. These PI substitutions did not affect the susceptibility of isolates to ABC or 3TC.

The effect of ABC resistance-associated amino acid substitutions on susceptibility to NRTIs and NNRTIs was determined. Isolates containing ABC resistance-associated substitutions singly, or in combination were susceptible to ZDV with the median FCs ranging from 0.3 to 0.6. ABC resistance-associated substitutions, K65R, K65R + M184V, and L74V + M814V conferred resistance to ddI and ddC. However, substitutions L74V, or M184V/I alone did not confer resistance to ddI. This result is surprising since the substitution L74V is known to confer resistance to ddI. The substitution M184V/I alone conferred resistance to ddC. Except for the K65R substitution, all other ABC-resistance associated substitutions did not confer resistance to TFV. However, the substitution M184V increased the susceptibility of K65R containing isolates to TFV. None of the ABC resistance-associated substitution alone, or K65R + M184V or L74V + M184V substitutions in combination decreased the susceptibility of isolates to the NNRTIs tested (DLV, EFV, and NVP).

METHODOLOGY

Clinical Sample Collection, Shipping, and Handling Information

Plasma samples were collected, stored and shipped to the [redacted] Subject samples identified for analysis were requested from [redacted] and shipped either to GlaxoSmithKline (GSK) International Clinical Virology Dept, Stevenage, UK for genotype determination or to [redacted] for drug susceptibility testing.

Methodology for Genotypic Analysis

All genotypic analyses were carried out at GSK by trained scientific staff using the In brief, viral RNA was purified from

sequence assembly was carried out by the Although the recommended lower number of copies of HIV RNA for use with this kit is 2000 copies, values down to 500 copies were tested in order to obtain a data set comparable to the Virologic phenotyping data set.

Methodology for Phenotypic Analysis

All phenotypic data were generated under The susceptibility of the HIV-1 RT coding region to select RT inhibitors was assessed using a recombinant virus assay Briefly, HIV RNA is purified

plotted as an inhibition curve. The inhibition curve of the subject's virus is compared to that of a drug-sensitive reference virus for each drug. The results from this assay are expressed as an IC_{50} (concentration of drug that inhibits the virus by 50%) value. If the virus requires a significantly higher drug concentration to inhibit the virus to the same degree as the drug sensitive reference virus, then it is considered to have reduced susceptibility to that drug (Petropoulos, 2000). Based on the fold-increase in IC_{50} concentration relative to the wild-type HIV-1 reference, samples were described as susceptible (<2.5-fold increase for most NRTIs and NNRTIs, <4.5 for ABC), resistant (≥2.5-fold for most NRTIs and NNRTIs, ≥4.5 for ABC).

Methodology for HIV RNA copy number determination:

The approved e used to determine HIV-1 copy number in all study participants plasma samples. The procedure is

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
sNDA 20, 977/SE2-012; sNDA 20, 978/SE2-014
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MICROBIOLOGY LABEL (07/29/04)

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted intracellularly by cellular enzymes to the active metabolite, carbovir triphosphate, 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. Abacavir is a weak inhibitor of cellular DNA polymerases α, β, and γ.

Antiviral Activity: The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The IC_{50} values of abacavir against different HIV-1 clades (A-E) ranged from 0.0015 to 1.0 μM, and against HIV-2 isolates, from 0.024 to 0.49 μM. Abacavir had synergistic activity in vitro in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, tenofovir, and zalcitabine. Ribavirin had no effect on the in vitro anti-HIV-1 activity of abacavir.

Resistance: HIV-1 isolates with reduced susceptibility to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from patients failing an abacavir-containing regimen demonstrated that amino acid substitutions K65R, L74V, Y115F, and M184V in HIV-1 RT contributed to abacavir resistance. In a study of therapy-naïve adults receiving ZIAGEN 600 mg once daily

(n=384) or 300 mg twice daily (n=386), in a background regimen of lamivudine 300 mg once daily and efavirenz 600 mg once daily (Study CNA30021), the incidence of virologic failure at 48 weeks was similar between the two groups (11% in both arms). Genotypic (n = 38) and phenotypic analyses (n = 35) of virologic failure isolates from this study showed that the RT mutations that emerged during abacavir once- daily and twice- daily therapy were K65R, L74V, Y115F, and M184V/I. The mutation M184V/I was the most commonly observed mutation in virologic failure isolates from patients receiving abacavir once daily (56%, 10/18) and twice daily (40%, 8/20).
Thirty-nine percent (7/18) of the isolates from patients who experienced virologic failure in the abacavir once-daily arm had a >2.5-fold decrease in abacavir susceptibility with a median fold decrease of 1.3 (range 0.5- to 11) compared to 29% (5/17) of the failure isolates in the twice daily arm with a median fold decrease of 0.92 (range 0.7- to 13).
Cross-Resistance: Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors (NRTIs). Recombinant laboratory strains of HIV-1_{HXB2} containing multiple abacavir resistance-associated mutations, namely, K65R, L74V, M184V, and Y115F, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in vitro. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. An increasing number of thymidine analogue mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

REFERENCES

Buckheit, R.W., and Swanstrom, R. Characterization of an HIV-1 isolate displaying an apparent absence of virion associated reverse transcriptase activity. AIDs Res Hum Retroviruses.1991, 7: 295-302.

Daluge, S.M, Good S.S., Faletto, M.B., Miller, W.H., St.Clair, M.H., Boone, L.R., Tisdale, M., Parry, N.G., Reardon, J.E., Dornsief, R.R., Averett, D.R., and Krenitsky, T. R. 1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity. Antimicrob. Agents and Chemother. 1997; 41:1082-1093.

Faletto, M.B. Intracellular metabolism of 1592U89, 139U91, and 1144U88 ((-)carbovir) in human CEM-T4 cells. Glaxo Wellcome report TEIN/94/0009. 1994. NDA 20-977; 4.1: 180-197.

Faletto, M.B. Effect of 1592U89 on the incorporation of ^{3}H-thymidine into human CEM-T4 cell DNA. Glaxo Wellcome report TEIN/94/0038. 1994. NDA 20-977; 4.1: 213-224.

Faletto, M.B., Miller, W.H., Garvey, E.P., St.Clair, M.H., Daluge, S.M., and Good, S.S. Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. Antimicrob. Agents and Chemother. 1997, 41:1099-1107.

GlaxoSmithKline Document Number SM2003/0014/00. CNA 30021 Virology Report: Analyses of HIV genotypic and phenotypic data collected during the course of clinical study CNA30021: A Phase III, 48-week, randomized, double-blind, multicenter study to evaluate the safety and efficacy of abacavir (ABC) 600mg once-daily (OAD) vs abacavir 300mg BID in combination with lamivudine (3TC, 300mg OAD) and efavirenz (EFV, 600mg OAD) in antiretroviral therapy naïve HIV-1 infected subjects. NDA 20-977/SE2-012, Vol 5, Pages 1-737.

GlaxoSmithKline Document Number RH2004/00089/00. Evaluation of two antiviral compounds against a panel of HIV-1 and HIV-2 virus isolates in fresh human PBMCs. NDA 20-977/SE2-012, 2004 (06/16/04).

GlaxoSmithKline Document Number RH2004/00060/00. Anti-HIV-1 effects of abacavir/lamivudine mixtures in combination with approved anti-HIV agents in MT-4 cells. NDA20-977/SE2-012, 2004 (06/16/04).

GlaxoSmithKline Document Number RH2004/00092/00. Anti-HIV-1 effects of abacavir, lamivudine,or emtricitabine in combination with ribavirin in MT-4 cells.NDA20-977/SE2-012,2004 (06/25/04).

GlaxoSmithKline Document Number RH2004/00088/00. Resistance and cross-resistance analyses of clinical isolates relevant to abacavir plus lamivudine combination therapy. NDA20-977/SE2-012, 2004 (06/16/04).

Harris, M., Back, D.,Kewn, S., Jutha, S., Marina, R. M., and Montaner, J.S.G. Intracellular carbovir triphosphate levels in patients taking abacavir once a day. AIDS, 2002:16:1196-97

Harrigan, P.R., Stone, C., Griffin, P., Najera, I., Bloor, S., Kemp, S.,Tisdale, M., and Larder, B. Resistance profile of the human immunodeficiency virus type 1 reverse transcriptase inhibitor abacavir (1592U89) after monotherapy and combination therapy. Journal of Infectious Diseases 2000,181:912-920.

Hill, A.V.(1910) The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. J. Physiol. (London), 40:4-8.

Kimpton J. and Emerman M. (1992) Detection of replication-competent and pseudotyped human immunodeficiency virus with a sensitive cell line on the basis of activation of an integrated β-galactosidase gene. J. Virol. 66(4):2232-2239.

Larder, B.A., Kohli, A., Kellam, P., Kemp, S.D., Kronick, M., and Henfrey, R.D., Quantitative detection of HIV-1 drug resistance mutations by automated DNA sequencing. Nature. 1993; 365: 671-673.

Lee, H., Hanes, J., and Johnson, K.A. Toxicity of nucleoside analogues used to treat AIDS and the selectivity of the mitochondrial DNA polymerase. Biochemistry, 2003, 42:14711-14719.

Mager ME. (1972) Data analysis in biochemistry and biophysics. New York: Academic Press.

Miller, V., Khaled-ait, M., Stone, C., Griffin, P., Mesogiti, D., Cutrell, A., Harrigan, R, Staszewski, S., Katlama, C., Pearce, G., and Tisdale, M. HIV-1 reverse transcriptase (RT) genotype and susceptibility to RT inhibitors during abacavir monotherapy and combination therapy. AIDS 200,14:163-171.

Parker, W. B., White, E.L., Shaddix, S.C., Ross, L. J., Buckheit, R.W. Jr , Germany, J.M., Secrist, J. A. III, Vince, R., and Shannon, W.M. Mechanism of inhibition of human immunodeficiency virus type 1 reverse transcriptase and human DNA polymerases α, β, and γ by the 5'-triphosphates of carbovir, 3'-azido-3'-deoxythymidine, 2',3'-dideoxyguanosine, and 3'-deoxythymidine. J. Biol.Chem. 1991;266:1754-1762.

Parry, N., and Tisdale, M. Anti-HIV activity of 1592U89. Glaxo Wellcome report BUEH/93/0001. 1993. NDA 20-977; 4.1: 14-18.
Pauwels R., De Clercq E., Desmyter J., Balzarini J., Goubau P., Herdewijn P., et. al. Sensitive and rapid assay on MT-4 cells for detection of antiviral compounds against the AIDS virus. J. Virol. Meth.1987, 16(3):171-185

Petropolous, C J., Parkin, N T., Kuniku, KL., Lie, Y S., Wrin, T., Huang, W., Tian, H., Smith, D., Winslow, GA., Capon, DJ., Whitcomb, JM. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. Antimicrob. Agent and Chemother. 2000; 44: 920-928.

Reardon, J.E. and Miller, R.H. Human immunodeficiency virus reverse transcriptase: substrate and inhibitor kinetics with thymidine 5'-triphosphate and 3'-azido-3'-deoxythymidine 5'-triphosphate. J. Biol. Chem 1990; 265: 202303-7.

Reardon, J.E. Human immunodeficiency virus reverse transcriptase: steady–state and pre-steady-state kinetics of nucleotide incorporation. Biochemistry 1992; 31: 4473-9.

Reardon, J.E. Substrate and inhibitor kinetics of 1144U88-triphosphate (705U90) and 1592U89-triphosphate (573U90) with HIV-1 reverse transcriptase. Glaxo Wellcome report TEZZ/93/0009-02. 1993. NDA 20-977; 4.1:245-256.

Reardon, J. E. Inhibition of human DNA polymerases α, β, γ and ε by the triphosphates of ddG (112Y84), 1144U88, ddA (111Y84), 1592U89, ddT (32Y81), and AZT (509U81). GlaxoWellcome report TEZZ/94/0007-0. 1994. NDA 20-977; 4.1:257-269.

Selleseth DW, Talarico CL, Miller T, Lutz MW, Biron KK and Harvey RJ. Interactions of 1263W94 with other antiviral agents in inhibition of human cytomegalovirus replication. Antimicrob. Agents Chemother.2003, 47:1468-71.

Shafer, R,W. Genotypic testing for human immunodeficiency virus type 1 drug resistance. Clin. Microbiol. Rev. 2002:15: 247-277.

Shafer, R,W. Stanford University Drug Resistance Database, resistance notes (2002). http://hivdb.stanford.edu/

St. Clair, M. Anti-HIV-1 activity of 1592U89. Glaxo Wellcome report TCZZ/94/0009, 1994. NDA 20-977; vol 4.1; 4-13.

Tisdale, M., Alnadaf, T., and Cousens, D. Combination of mutations in human immunodeficiency virus Type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89. Antimicrob. Agents and Chemother.1997; 41: 1094-1098

Tisdale, M., and Cousens, D. Studies on the development of resistance to 1592U89 by in vitro passage. Glaxo Wellcome report BUMA/93/0006. 1994. NDA 20-977; 4.1:19-25.

Tisdale, M., and Selway, J.W.T. Antiviral spectrum of 1592U89. Glaxo Wellcome report BUIA/94/0001. 1994. NDA 20-977; 4.1:26-32.

PHASE IV COMMITMENTS

RECOMMENDATIONS

With respect to microbiology, sNDA # 20-977/SE2-012 and sNDA # 20-978/SE2-014 are approvable.

Lalji Mishra, Ph.D.
Microbiologist

CONCURRENCES:

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)
sNDA 20, 977/SE2-012; sNDA 20, 978/SE2-014
Reviewer: LALJI MISHRA, Ph.D. **Review Completed: 07/08/04**

_____ Date_____
HFD-530 /J. Farrelly/Assoc Dir

_____ Date_____
HFD-530/J. O'Rear /TL Micro

CC:
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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-977 (SE2-012); 20-978 (SE2-014)
GENERIC NAME: Abacavir sulfate
TRADE NAME: Ziagen
FORMULATIONS: 300 mg tablet;
20 mg/mL solution
APPLICANT: GlaxoSmithKline
LETTER DATE: 10/02/2003
DATE RECEIVED: 10/03/2003

REVIEWERS: Jenny H. Zheng, Ph.D.
TEAM LEADER: Kellie S. Reynolds, Pharm.D.
PHARMACOMETRIC REVIEWER: J. H. Zheng, Ph.D.
Secondary PM Review by Joga Gobburu, Ph.D.
OCPB DIVISION: DPE3 (HFD-880)
CLINICAL DIVISION: Division of Antiviral Drug Products (HFD-530)

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- Pharmacometric consult- NOT APPLICABLE

1.0 EXECUTIVE SUMMARY

Ziagen (abacavir sulfate) is a nucleoside reverse transcriptase inhibitor that is indicated for the treatment of HIV-1 infection, in combination with other antiretroviral agents. The approved dosing regimen in adults is 300 mg BID. The applicant submitted the current efficacy supplement in support of a 600 mg QD dosing regimen.

1.1 RECOMMENDATIONS

The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant for NDA 20-977 (SE2-012) and NDA 20-978 (SE2-014) is acceptable. The Phase IV commitments listed below need to be addressed.

1.2 PHASE IV COMMITMENTS

1. The applicant commits to provide human pharmacokinetic information on plasma abacavir concentrations and intracellular carbovir triphosphate [CBV-TP] concentrations following administration of abacavir 600 mg once daily.

The applicant did not provide exposure data following administration of abacavir 600 mg QD. However, data are available following administration of a single 600 mg dose. The literature contains some plasma pharmacokinetic data following administration of abacavir 600 mg QD, but no intracellular carbovir triphosphate data at that dose. Because the supplement includes a large Phase 3 safety and efficacy study of the 600 mg QD dose, the plasma and intracellular pharmacokinetic data were not essential to approval of the application. However,

the review team believes that such information may aid the interpretation of the relationship between CBV-TP concentrations and the development of resistance.

[illegible] patients who received abacavir plus stavudine, based on the population pharmacokinetic analysis.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Ziagen (abacavir sulfate) is a nucleoside reverse transcriptase inhibitor that is indicated for the treatment of HIV-1 infection, in combination with other antiretroviral agents. The approved dosing regimen in adults is 300 mg BID. The applicant submitted the current efficacy supplement in support of a 600 mg QD dosing regimen. Study CNA30021 provided the efficacy and safety data for the 600 mg QD regimen. Study CNA30021 was an international, multicenter, double-blind, controlled study in 770 HIV-infected, therapy naïve adults. The study included two treatment arms, abacavir 600 mg QD vs. abacavir 300 mg BID, both in combination with lamivudine 300 mg QD + efavirenz 600 mg QD.

The majority of the clinical pharmacology information for abacavir is included in the original review for NDA 20977 and NDA 20978 (December 11, 1998; Prabhu Rajagopalan, Ph.D.). The applicant included one clinical pharmacology study report (CNA10905) and a population pharmacokinetic report in this supplement.

Study CNA10905 was an open-label, single arm, pharmacokinetic, pilot study. The study included patients taking ZIAGEN (300mg abacavir) BID or TRIZIVIR (300mg abacavir/150mg lamivudine/300mg zidovudine) BID, in combination with other antiretroviral medications. Steady-state abacavir plasma concentrations and carbovir triphosphate (CBV-TP) intracellular concentrations were determined. On the day that PK samples were collected, the evening dose was held, to allow a 24-hour assessment of CBV-TP elimination half-life. The results of the study indicated that abacavir plasma concentrations and CBV-TP intracellular concentrations were lower than observed in previous studies. The applicant did not provide an explanation for the lower concentrations. The mean intracellular CBV-TP C_{24} (16 fmol/10^6 cells or approximately 32 nmol/L) in this study were higher than the reported Ki value for HIV-1 RT catalyzed incorporation of dGTP into DNA (21 nmol/L, [Daluge, 1997]) throughout the 24 h interval. The sponsor did not estimate the C_{24} of abacavir or CBV-TP after 600 mg abacavir once daily. The observed intracellular CBV-TP concentrations and its terminal half-life of 20.64 hours support the clinical investigations of the use of abacavir once daily for the treatment of HIV infected patients. However, clinical data were needed in order to determine whether once daily abacavir administration is effective. Such data were provided by study CNA30021. Study CNA30021 was reviewed by the Clinical and Statistics reviewers.

The applicant did not provide exposure data following administration of abacavir 600 mg QD. However, data are available following administration of a single 600 mg dose. The literature contains some plasma pharmacokinetic data following administration of abacavir 600 mg QD, but no intracellular CBV-TP data at that dose. Because the supplement includes a Phase 3

safety and efficacy study of the 600 mg QD dose, the plasma and intracellular pharmacokinetic data were not essential to approval of the application. However, the review team believes that such information may aid the interpretation of the relationship between CBV-TP concentrations and the development of resistance. As a Phase 4 commitment, the applicant will be asked to provide plasma abacavir and intracellular CBV-TP concentration data, following administration of abacavir 600 mg QD.

The applicant submitted a population-based pharmacokinetic analysis in response to a previous Phase IV commitment. The analysis included an evaluation of the effect of gender, race, and concomitant medications on abacavir pharmacokinetics. The results indicate that gender does not have a significant effect on abacavir pharmacokinetics, when the results are adjusted for lean body weight. The results also indicate that abacavir pharmacokinetics do not differ between Black and White patients. The concomitant use of didanosine was associated with a 19% increase in abacavir clearance. Based on previous efficacy information, the increase in abacavir clearance is not significant. However, the results also indicate that concomitant use of stavudine was associated with a 38% decrease in abacavir clearance. The decreased clearance could lead to a 61% increase in abacavir exposure. The applicant will be asked to evaluate the available safety data for the combination of abacavir plus stavudine.

2.0 QUESTION-BASED REVIEW

2.1 General Attributes

Other than dosing regimen information, no new general information was submitted with this supplement. See the original review of NDAs 20-977 and 20-978.

2.1.1 What is the proposed indication?

ZIAGEN, in combination with other antiretroviral agents, is indicated for treatment of HIV-1 infection. The indication did not change based on the current supplement.

2.1.2 What are the proposed dosing regimens for abacavir?

Based on the current supplement, the following dosing regimen is proposed for adults- ZIAGEN 600 mg once daily, in combination with other antiretroviral agents.

The following regimen, previously approved, is also in the label- ZIAGEN 300 mg twice daily, in combination with other antiretroviral agents.

2.2 General Clinical Pharmacology

The majority of the clinical pharmacology information for abacavir is included in the original review for NDA 20977 and NDA 20978. The questions for which new information was provided in the current supplement are answered below.

2.2.1 What are the design features of the pivotal clinical trials?

Study CNA30021 provided the efficacy and safety data for the 600 mg QD regimen. Study CNA30021 was an international, multicenter, double-blind, controlled study in 770 HIV-infected, therapy naïve adults. The study included the following treatment arms.

Abacavir 600 mg QD + lamivudine 300 mg QD + efavirenz 600 mg QD

Abacavir 300 mg BID + lamivudine 300 mg QD + efavirenz 600 mg QD

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, the applicant measured the appropriate moieties in clinical pharmacology studies. They measured abacavir in all clinical pharmacology studies. In addition, they determined intracellular carbovir triphosphate (active moiety) concentrations in study CNA10905.

2.2.3 Exposure-response evaluations

The current supplement does not include any new exposure-response information. The original NDA submission included evaluations of abacavir doses ranging from 200 mg BID to 600 mg TID. Based on those evaluations, the applicant selected a dose of 300 mg BID for Phase III clinical trials.

Based on data that indicate the half-life of intracellular CBV-TP is approximately 20 hours, the applicant determined that once-daily dosing of abacavir was feasible. Thus, they conducted Study CNA30021. The decision regarding approval of the once daily dosing regimen is based on the 48-week safety and efficacy data from Study CNA30021.

2.2.4 Pharmacokinetic characteristics of abacavir

The pharmacokinetic characteristics of abacavir are described in the original review of NDAs 20977 and 20978. The applicant submitted the results of one clinical pharmacology study to the current supplement. Study CNA10905 was conducted in twenty HIV infected patients who were on a stable abacavir containing regimen (300 mg BID). The plasma abacavir and intracellular CBV-TP concentrations were determined. On the day of pharmacokinetic sampling, the second abacavir dose was not administered, so the intracellular CBV-TP elimination half-life (T1/2) could be determined.

The following table summarizes plasma PK parameters of abacavir from study CNA10905.

Abacavir PK parameters

Parameter	Geometric Mean (N=20)	95 % CI
$AUC_{0-24,ss}$, (µg·h/mL)	2.56	2.13 – 3.06
$C_{max,ss}$, (µg/mL)	0.88	0.75 – 1.03
$t_{½}$, (h)	2.59	2.04 – 3.29
$t_{max,ss}$,[a] (h)	2.00	2.0 – 3.92

a. $t_{max,ss}$ is presented as median and range.

The observed abacavir plasma concentrations were lower than those previously observed in HIV infected patients after abacavir 300 mg BID (C_{max} = 3.0 µg/mL and AUC_{12} = 6.02 µg·hr/mL). The sponsor concluded that the observed abacavir pharmacokinetics were similar to those previously observed in HIV infected patients. It is unclear what the basis is for their conclusion. The terminal T1/2 observed in this study was slightly longer compared to the approximately 1.5 hour T1/2 that is typically observed. The sponsor states that this difference was likely due to differences in the blood sampling schedule, which was through 24 hours in the current study compared to 12 hours in previous studies, which is reasonable.

Intracellular CBV-TP PK parameter estimates are summarized in the table below.

CBV-TP PK parameters

Parameter	Geometric Mean (N=20)	95 % CI
$AUC_{0\text{-}24,ss}$, (fmol*h/10^6cells)	252.78	190.05 – 336.21
$C_{max,ss}$ (fmol/10^6cells)	29.66	22.07 – 39.86
$t_{½}$, (h)	20.64	16.39 – 25.99
	Median	**Min – Max**
$C_{tau,ss}$ (C_{12}), (fmol/10^6cells)	18.1	4.7 – 51.6
C_{24}, (fmol/10^6cells)	16.35	3.1 – 61.1
$t_{max,ss}$, h	2.00	0.00 – 12.00

The data show that intracellular CBV-TP has a prolonged terminal half-life compared to plasma abacavir, with a geometric mean of 21 hours. CBV-TP concentrations were lower in this study compared to those reported by Kewn [2000] and Harris [2001]. These two studies were presented as posters at conferences. The applicant did not describe the details of these two studies. The applicant indicated that the difference may be due to several factors, including the small number of subjects in the two earlier studies, differences in cell processing, and differences in assay methodology (non GLP template primer binding assay versus GLP specific LC/MS/MS). However, it could also be related to the low plasma abacavir concentrations observed in this study.

Although the plasma abacavir and intracellular CBV-TP concentrations were lower than those observed in other studies, the intracellular CBV-TP elimination half-life supported further evaluation of a once-daily abacavir regimen.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure or response to abacavir? What is the impact of these factors on exposure and response?

The applicant submitted a population-based pharmacokinetic analysis, in response to a Phase IV commitment. The analysis included an evaluation of the effect of gender and race on abacavir pharmacokinetics. The results indicate that gender does not have a significant effect on abacavir pharmacokinetics, when the results are adjusted for lean body weight. The results also indicate that abacavir pharmacokinetics do not differ between Black and White patients.

2.4 Extrinsic factors

2.4.1 What are the extrinsic factors that influence exposure or response?

The applicant submitted a population-based pharmacokinetic analysis, in response to a Phase IV commitment. The analysis included an evaluation of the effect of concomitant medications on abacavir pharmacokinetics.

The results indicate that concomitant use of didanosine was associated with a 19% increase in abacavir clearance. Based on previous efficacy information, the increase in abacavir clearance is not significant.

The results indicate that concomitant use of stavudine was associated with a 38% decrease in abacavir clearance. The decreased clearance could lead to a 61% increase in abacavir exposure (AUC). The applicant will be asked to evaluate the available safety data for the combination of abacavir plus stavudine.

2.5 General Biopharmaceutics

The applicant did not submit any biopharmaceutics information with this NDA supplement. See the original review of NDA 20-977 and 20-978.

2.6 Analytical section

Assay validation and performance was acceptable. See the individual study review for details.

3.0 LABELING RECOMMENDATIONS

Based on the current supplement, the applicant changed the following sections.

CLINICAL PHARMACOLOGY

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 ± SD) and $AUC_{(0\text{-}12\ hr)}$ was 6.02 ± 1.73 mcg•hr/mL. After oral administration of a single dose of 600 mg of abacavir in 20 patients, C_{max} was 4.26 ± 1.19 mcg/mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hr/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.

Reviewer Notes: The applicant added the 600 mg single dose information, which was based on information submitted with the original NDA in 1998; the information is acceptable.

The applicant added information about intracellular carbovir triphosphate to the Metabolism subsection. The general information is in the Microbiology section, so we asked them to delete it from the Metabolism subsection. Also, we asked them to delete the carbovir triphosphate half-life, because that information can be misinterpreted and is not included in NRTI labels. The applicant agreed to the changes.

Gender: A population pharmacokinetic analysis in HIV-infected male (n=304) and female (n=67) patients showed no gender differences in abacavir AUC normalized for lean body weight.
Race: There are no significant differences between blacks and Caucasians in abacavir pharmacokinetics

Reviewer Note: The above information was added, based on the population pharmacokinetic report submitted on June 17, 2003.

4.0 APPENDICES-

Individual Study Reviews

Study CNA10905 (Page 10)
Population Pharmacokinetic Report (Page 13)

Final Label

CLINICAL PHARMACOLOGY SECTION (Page 41)

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

/s/

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8/2/04 01:07:03 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-977 / S-012
20-978 / S-014

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-977

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	300 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,034,394	7/23/1991	12/18/2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-2723	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

1.4.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingrecient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration.
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-977

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	300 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 1. Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

1.4.1 Patent Information

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-977

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	300 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 2. Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

1.4.1 Patent Information

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-977

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	300 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (If patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 4 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

1.4.1 Patent Information

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-977

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	300 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 6 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

1.4.1 Patent Information

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

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INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-977

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	300 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 7 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

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Food and Drug Administration
CDER (HFD-007)
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Rockville, MD 20857

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INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

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2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
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NAME OF APPLICANT / NDA HOLDER
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TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	300 mg

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,294,540 B1	9/25/2001	5/14/2018

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.1 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 3 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

1.4.1 Patent Information

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-978

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	20 mg/mL

DOSAGE FORM
oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,034,394	7/23/1991	12/18/2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-2723	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.2 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)* — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-978

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	20 mg/mL

DOSAGE FORM
oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.2 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 1. Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-978

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	20 mg/mL

DOSAGE FORM
oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.2 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 2. Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-978

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	20 mg/mL

DOSAGE FORM
oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.2 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-978

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	20 mg/mL

DOSAGE FORM
oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.2 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 6 — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
20-978

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	20 mg/mL

DOSAGE FORM
oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,089,500	2/18/1992	6/26/2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.2 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingred ent described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 7 — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857.

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
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See OMB Statement on Page 3.

NDA NUMBER
20-978

NAME OF APPLICANT / NDA HOLDER
GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ZIAGEN

ACTIVE INGREDIENT(S)	STRENGTH(S)
abacavir sulfate	20 mg/mL

DOSAGE FORM
oral solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,294,540 B1	9/25/2001	5/14/2018

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corporation	Corporate Intellectual Property Five Moore Drive	
	City/State Research Triangle Park, NC	
	ZIP Code 27709	FAX Number *(if available)* 919-483-7988
	Telephone Number 919-483-7656	E-Mail Address *(if available)* david.j.levy@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

1.4.2 Patent Information

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 3. — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
David J. Levy	SEPTEMBER 24, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name David J. Levy, Ph.D. Patent Counsel GlaxoSmithKline	
Address Five Moore Drive	City/State Research Triangle Park, NC
ZIP Code 27709	Telephone Number 919-483-2723
FAX Number *(if available)* 919-483-7988	E-Mail Address *(if available)* david.j.levy@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY for NDA #: 20-977 and 20-978 SUPPL #: S-012 and S-014
Trade Name: ZIAGEN®
Generic Name: abacavir sulfate, tablets and oral solution
Applicant Name: GlaxoSmithKline
Approval Date:
HFD-530: Division of Antiviral Drug Products

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 questions 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.)? SE2

   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 / X /NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 (three)

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

   YES / X /NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /__/ NO /_X_/

   If yes, NDA #: _____ Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

   YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X_/ NO /___/

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

   NDA #: **20-977 ZIAGEN (abacavir sulfate, tablets)**

NDA #: **20-978 ZIAGEN (abacavir sulfate, oral solution)**

NDA #: **21-205 Trizivir (abacavir sulfate, lamivudine and zidovudine)**

2. Combination product. **N/A**
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 9. 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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 / X / 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 9:**

(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 / X / 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 / X /

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 / X /

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:

Investigation #1, Study # **CNA30021**

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 / X /

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

   NDA # _____Study #
   NDA # _____Study #
   NDA # _____Study #

   (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 / X /

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

   NDA # _____Study #
   NDA # _____Study #
   NDA # _____ Study #

   (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"):

Investigation #1, Study # **CNA30021**

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 # 45,331 YES / X / 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 / X /

If yes, explain: _____

_____

_____

Additional comment:

_____

Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Debra Birnkrant
8/13/04 02:40:55 PM

EXCLUSIVITY SUMMARY for NDA #: 20-977 and 20-978 SUPPL #: S-012 and S-014
Trade Name: ZIAGEN®
Generic Name: abacavir sulfate, tablets and oral solution
Applicant Name: GlaxoSmithKline
Approval Date:
HFD-530: Division of Antiviral Drug Products

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 questions 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.)? SE2

   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 / X /NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3 (three)

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

   YES / X /NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /__/ NO /_X_/

   If yes, NDA #: _____ Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

   YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X_/ NO /___/

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

NDA #: **20-977 ZIAGEN (abacavir sulfate, tablets)**

NDA #: **20-978 ZIAGEN (abacavir sulfate, oral solution)**

NDA #: **21-205 Trizivir (abacavir sulfate, lamivudine and zidovudine)**

2. Combination product. **N/A**
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 9. 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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (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 / X / 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 9:**

   (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 / X / 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 / X /

   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 / X /

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:

Investigation #1, Study # **CNA30021**

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 / X /

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 / X /

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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"):

Investigation #1, Study # **CNA30021**

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 # 45,331 YES / X / 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 / X /

If yes, explain: _____

Additional comment:

Signature of Preparer Date Aug 9, 2004
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 20-977 and NDA 20-978 Supplement Type (e.g. SE5): SE2 Supplement Number: S012 and S014, respectively

Stamp Date: October 3, 2004
Action Date: August 2, 2004

HFD- 530

Trade and generic names/dosage form: ZIAGEN® (abacavir sulfate) tablets and oral solution

Applicant: GlaxoSmithKline **Therapeutic Class:** Antiretroviral/nucleoside analog. (7030241)

Indication(s) previously approved: Treatment of HIV-1 infection

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s):1

Indication #1: Treatment of HIV-1 infection

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.

✔ No: Please check all that apply: ✔ Partial Waiver ✔ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo. 0	yr._____	Tanner Stage_____
Max_____	kg_____	mo.< 3	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ✔ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ✔ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.** 3	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 17	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ✔ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Tanima Sinha, M.S., Regulatory Project Manager

cc: NDA 20-977 (S-012) and NDA 20-978 (S-014)
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Virginia Behr
8/12/04 12:06:27 PM

NDA 20-977
ZIAGEN® (abacavir sulfate) Tablets

Supplemental New Drug Application
600mg Once-Daily Dosing Regimen

DEBARMENT CERTIFICATION

GlaxoSmithKline 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.

21 AUG 2003

Charles E. Mueller
Director, North America Clinical Compliance
Worldwide Regulatory Compliance

Date