

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-652

MEDICAL REVIEW

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/mm³ in the group receiving abacavir 600 mg once daily and 200 cells/mm³ 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)

- 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 applicant and the applicant has committed to providing this human PK information on ZIAGEN given 600 mg once daily (see below under Phase IV commitments).*
- 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.*
 - *Further, the applicant has also committed to submitting another study (ESS101822) which will address the increased HSR severity issue as a Phase IV commitment (see below).*
 4. **Pediatrics and once daily dosing.** Ziagen is available in oral solution for use in pediatric patients. As the 600 mg once daily dosing regimen becomes available for the adults, PK and safety information for once daily use in children will need to be addressed.
 - *This issues has been addressed with the applicant and the applicant has committed to providing PK and safety data for once daily dosing in children 2 to 13 years of age (this study is currently ongoing in Europe)*

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

1. 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: Submit results by November 30, 2004.

Additional post-marketing commitment: Pediatrics

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 (ZIAGEN once daily regimen).

The deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered required postmarketing study commitment. The status of this postmarketing pediatric study shall be reported annually according to 21 CFR 314.81. The pediatric commitment for this application is: deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 3 months to 17 years with the final report submission date of December 31, 2007.

**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 as 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"*
- *A usage statement will be added for all abacavir-containing package inserts as follows: 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.*
- *As the Office of Drug Safety consultation has recommended, a Dear Health Care Provider Alert letter at the time of the EZICOM launch will be recommended to the applicant as a phase IV commitment. This letter should contain wording that encourages the healthcare provider to report ABC-HSR to the already established HSR registry.*
- *A study that assesses the effectiveness of the Medguides and Warning Cards of the abacavir-containing products will be recommended to the applicant as a phase IV commitment*
- *A variety of educational programs which targets the prescribers as well as the patients (i.e. patient educational slide kits) has been proposed by the applicant. An annual assessment of the progress of such educational activities will be important and the applicant will be asked to provide such annual assessments to the Agency for the first few years after the launch of this FDC product.*
- *The applicant will be asked to enhance their passive surveillance. HSR adverse event report summaries (for all abacavir-containing products) will need to be submitted in quarterly intervals and all serious hypersensitivity reactions and hypersensitivity reactions resulting from the reintroduction of abacavir should be reported in an expedited manner (i.e., as 15-day reports).*

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.

- *To address this important efficacy concern, a usage statement will be inserted in the EZICOM package insert INDICATIONS and USAGE section as follows: As part of a triple-drug regimen, EZICOM tablets are recommended for use with antiretroviral agents from different pharmacological classes and not with other nucleoside/nucleotide reverse transcriptase inhibitors.*
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.
- *This issue has been addressed with the applicant and the applicant has committed to providing this 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)*

Applicant's Phase IV commitments for NDAs 21,652: EPZICOM™

1. 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 600mg once daily abacavir vs. 300mg twice daily abacavir (in combination with other drugs). Submit an analysis of genotypic and phenotypic results of study CAL30001 and submit these data in Division of Antiviral Drug Products (DAVDP's) HIV Resistance Template Format.

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

2. Assess phenotypes for baseline HIV-1 isolates from all patients in clinical study CAL30001, a study comparing 600mg once daily abacavir vs. 300mg twice daily abacavir (in combination with other drugs). Submit phenotypic data in DAVDP's HIV Resistance Template Format.

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

3. Draft a "Dear Healthcare Provider" letter for submission to DAVDP for review and comment, followed by distribution of this letter soon after approval of this product. As in previous letters to healthcare providers, the draft letter should encourage providers to report hypersensitivity reactions and provide telephone numbers and other contact information for reporting reactions to GlaxoSmithKline and MedWatch.

Timeline: Submit a draft letter to DAVDP for review and comment within 15 days of the date of this letter.

4. Evaluate practical aspects of use of the Medication Guide and Warning Card in order to obtain information on the utility of these sources of information for patients. Specific questions to be addressed in a study are (a) Do patients receive the Medication Guide and Warning Card? (b) Do patients read the Medication Guide and Warning Card? (c) Do patients understand why they receive a Medication Guide and Warning Card? (d) Do patients take action (e.g., ask their doctor or pharmacist follow-up questions) based on the Medication Guide and Warning Card?
 - a. Submit a proposal for this evaluation within 6 months of the date of this letter
 - b. Submit a final report within 30 months of the date of this letter.
5. Conduct a multifaceted educational program to communicate the important risk information about potential hypersensitivity reactions to abacavir. Specific activities within this multifaceted educational program are listed below.
 - a. Introduce EPZICOM™ (abacavir/lamivudine) Tablet with the following activities directed to clinical investigators in future GSK-sponsored clinical studies on the abacavir/lamivudine tablet:
 - i. Protocols will include language describing the diagnosis and management of abacavir-related hypersensitivity reactions, consistent with information in FDA-approved labeling.
 - ii. Studies will continue to use a standard Case Report Form Module to facilitate collection of standardized information on cases of HSR.

- iii. All pre-study meetings with clinical investigators will include a discussion on reporting of adverse events, including attention to timely detection and reporting of hypersensitivity reactions.
- b. Introduce EPZICOM™ Tablet into US distribution channels with the following items intended for use by health care professionals with patients:
 - i. FDA-approved Medication Guide
 - ii. FDA-approved Warning Card
 - iii. A Patient Brochure providing general information on HIV infection and product-specific information on the abacavir/lamivudine tablet.
 - iv. Pads of tear-off sheets showing the full text of the Warning Card plus statements to highlight the names of three different products (ZIAGEN®, TRIZIVIR® and EPZICOM™) containing abacavir.
- c. Prepare and make available a slide kit, entitled "What You Need to Know About ZIAGEN®, TRIZIVIR®, EPZICOM™ and the Abacavir in Them". The audience for this slide kit is patients and the slide kit will be offered to community organizations and health care providers for use with patients. The proposed slide kit will be submitted to DDMAC for review and comment after the final labeling is approved by DAVDP.
- d. Organize and host a teleconference intended to provide information to patient community organizations for people living with HIV infection: This teleconference will occur after approval and prior to commercial availability of the product. The purpose of the teleconference is to summarize key information about this new product, including its abacavir content and contraindication for use in any patient with a history of hypersensitivity to abacavir.

Timeline: Submit an annual summary of the above educational programs concurrent with the deadline for the NDA Annual Report on the first and second anniversaries of the date of this letter

In addition to the above Phase IV commitments, the applicant has also agreed to the following:

Construct Periodic Reports of adverse drug experiences (per 21 CFR 314.80) such that reports of HSR with this product are analyzed and summarized in the context of all abacavir-containing prescription drug products (Ziagen, Trizivir, and this product). Periodic reports must also include a separate section on rechallenge cases of hypersensitivity to abacavir. (Timeline: Periodic Reports will be submitted on the schedule required by 21 CFR 314.80)

Additional post-marketing commitment: Pediatrics

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 (EPZICOM™). The deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered required postmarketing study commitment. The status of this postmarketing pediatric study shall be reported annually according to 21 CFR 314.81. The pediatric commitment for this application is: deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 3 months to 17 years with the final report submission date of December 31, 2007.

**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: These 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 trials; 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
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/s/

Rosemary Johann-Liang
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Revised TLMemo: Please sign off. Thanks.

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

Medical Officer's Review

NDA 21-652

Date submitted: October 7, 2003
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Draft Review completed: July 26, 2004
Final Review completed: August 2, 2004
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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: Generic: abacavir sulfate (EPZICOM® constituent)
Generic: lamivudine (EPZICOM ® constituent)
Trade: EPZICOM®

Route: Oral

Dosage form: Fixed dose combination tablet: abacavir 600mg/
lamivudine 300mg

Indication: Treatment of HIV infection

CLINICAL REVIEW

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Clinical Review for NDA 21-652

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Fixed-dose combination antiretroviral products (FDCs) and co-packs were identified as an important part of the WHO “3-by-5 initiative” (with the objective of providing lifelong antiretroviral therapy to 3 million people by the end of 2005) and President Bush's Emergency Plan for AIDS Relief (PEPFAR (with the objective of providing antiretroviral treatment to 2 million persons over the 5 year span of 2003-2008)). (WHO, 2003; The White House Fact Sheet, Jan 2003)

DHHS supports the efforts of PEPFAR and WHO. Specifically, on May 16, 2004, Secretary Thompson announced that FDA would issue a new guidance document to present regulatory details of a new expedited review process for regulatory applications for FDCs and co-packaged products. Secretary Thompson stated that “Fixed dose combination products and co-packaged products are an important tool in improving the quality of health care in developing nations”. On this same occasion, Acting Commissioner Crawford stated that “Drugs that are approved by FDA under the process described in the guidance will meet all FDA standards for drug safety, efficacy, and quality.” (DHHS, 2004; FDA 2004)

In addition, 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].

Towards the goal of simplifying therapy, GlaxoSmithKline (GSK) undertook a development program to combine abacavir (ZIAGEN™, abacavir sulfate, ABC) and lamivudine (3TC, EPIVIR™) into an FDC to be administered once daily.

In October 2003, GSK submitted the data from CNA30021, a large, randomized, double-blind, active-controlled, Phase 3 study, which provides evidence of safety, efficacy and durability of

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once daily ABC and 3TC as a nucleoside backbone combined with EFV in antiretroviral treatment (ART) naïve subjects. The comparator regimen (ABC BID + 3TC once daily (OAD) + EFV once daily) 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. Since both study arms contained 3TC once daily and EFV once daily, no conclusions could be made about either of their contributions to AEs.

In addition to CNA30021, GSK submitted one pharmacokinetic (PK) study, CAL10001, in support of this new drug application (NDA). CAL10001 was designed to demonstrate the bioequivalence between ABC/3TC (600mg/300mg) combination tablet versus ABC (2 x 300mg tablets) and 3TC (2 x 150mg tablets). CAL10001 did not contribute any efficacy data and the safety data were not unusual or unexpected for this drug combination.

Although the ABC/3TC FDC tablet was not used in CNA30021, the bioequivalence results from CAL10001 allow us to extrapolate that the ABC/3TC FDC is as effective and safe as the separate components of ABC 600mg + 3TC 300mg (the combination used in CNA30021). Therefore, from the clinical perspective, the 48 week efficacy and safety data presented in this NDA support the approval of FDC ABC/3TC once daily 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:

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Clinical Virology:

- a. Assess RT resistance mutations and phenotypes of HIV-1 isolates from patients who experience virologic failure at 24 or 48 weeks in clinical study CAL30001, a study comparing 600mg once daily abacavir vs. 300mg twice daily abacavir (in combination with other drugs). (Timeline: submit results of these assessments within 12 months of approval of NDA 21-652.)
 - b. Assess RT resistance mutations for baseline HIV-1 isolates from all patients in clinical study CAL30001, a study comparing 600mg once daily abacavir vs. 300mg twice daily abacavir (in combination with other drugs). (Timeline: submit results of these assessments within 12 months of approval of NDA 21-652.)
 - c. Assess phenotypes for baseline HIV-1 isolates from all patients in clinical study CAL30001, a study comparing 600mg once daily abacavir vs. 300mg twice daily abacavir (in combination with other drugs). Submit an analysis of genotypic and phenotypic results of study CAL30001 (as well as submit genotypic and phenotypic data in DAVDP's HIV Resistance Template Format). (Timeline: within 18 months of approval of NDA 21-652.)
2. Draft a "Dear Healthcare Provider" letter for submission to DAVDP for review and comment, followed by distribution of this letter soon after approval of this product. As in previous letters to healthcare providers, the draft letter should include text to encourage providers to report hypersensitivity reactions and provide telephone numbers and other contact information for reporting reactions to GlaxoSmithKline and MedWatch. (Timeline: submit a draft letter to DAVDP for review and comment within 15 days after approval of NDA 21-652)
 3. Evaluate practical aspects of use of the Medication Guide and Warning Card in order to obtain information on the utility of these sources of information for patients. Specific questions to be addressed in a study are (a) Do patients receive the Medication Guide and Warning Card? (b) Do patients read the Medication Guide and Warning Card? (c) Do patients understand why they receive a Medication Guide and Warning Card? (d) Do patients take action (e.g., ask their doctor or pharmacist follow-up questions) based on the Medication Guide and Warning Card?
 - a. Submit a proposal for this evaluation to DAVDP within 6 months after approval of this product.
 - b. Submit a report within 30 days of agreement with DAVDP on the study proposal.
 4. Conduct a multifaceted educational program to communicate the important risk information about potential hypersensitivity reactions to abacavir. Specific activities within this multifaceted educational program are listed below. (Timeline: Submit an annual summary of this educational program concurrent with the deadline for the NDA Annual Report on the first and second anniversaries of approval of the product.)

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- a. Introduce the abacavir and lamivudine (abacavir/lamivudine) tablet with the following activities directed to clinical investigators in future GSK-sponsored clinical studies on the abacavir/lamivudine tablet:
- Protocols will include language describing the diagnosis and management of abacavir-related hypersensitivity reactions, consistent with information in FDA-approved labeling.
 - Studies will continue to use a standard Case Report Form Module to facilitate collection of standardized information on cases of HSR.
 - All pre-study meetings with clinical investigators will include a discussion on reporting of adverse events, including attention to timely detection and reporting of hypersensitivity reactions.
- b. Introduce the abacavir/lamivudine tablet into US distribution channels with the following items intended for use by health care professionals with patients:
- FDA-approved Medication Guide
 - FDA-approved Warning Card
 - a Patient Brochure providing general information on HIV infection and product-specific information on the abacavir/lamivudine tablet.
 - Pads of tear-off sheets showing the full text of the Warning Card plus statements to highlight the names of three different products (ZIAGEN, TRIZIVIR and EPZICOM) containing abacavir.
- c. Prepare and make available a slide kit, entitled "What You Need to Know About ZIAGEN, TRIZIVIR, EPZICOM and the Abacavir in Them". The audience for this slide kit is patients and the slide kit will be offered to community organizations and health care providers for use with patients. GSK will strive to assure that the slide kit aligns with the patient-directed labeling in the Medication Guide and Warning Card. The proposed slide kit will be submitted to DDMAC for review and comment after the final labeling is approved by DAVDP.
- d. Organize and host a teleconference intended to provide information to patient community organizations for people living with HIV infection: This teleconference will occur after approval and prior to commercial availability of the product. The purpose of the teleconference is to summarize key information about this new product, including its abacavir content and contraindication for use in any patient with a history of hypersensitivity to abacavir.

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II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Product name: Abacavir sulfate/lamivudine fixed dose combination (ABC/3TC FDC, EPZICOM®)

Class: Antiretroviral drug

Subclass: Nucleoside reverse transcriptase analogue (NRTI)

Route: Oral

Formulation: 600mg/300 mg tablet

The data source for this review comes from the October 7, 2003 GSK submission. The submission includes data collected from one large pivotal clinical trial (Study CNA30021) and one supportive PK bioequivalence trial (Study CAL10001).

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 + 3TC 300 mg OAD in study CNA30021.

Supportive study CAL10001 was a bioequivalence PK study of ABC/3TC FDC (600mg/300mg) combination tablet versus ABC (2 x 300mg tablets) and 3TC (2 x 150mg tablets). A total of 30 subjects were enrolled in the study and all subjects received at least one dose of ABC/3TC FDC.

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

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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 change 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/mm³; ABC BID 200 cells/mm³).

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 susceptibility. Other common treatment emergent resistance mutations were NRTI-associated mutation, L74V and NNRTI-associated, K103N.

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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 supports the new FDC of ABC/3TC given once daily as an effective and generally well tolerated dose in HIV-1 infected patients.

GSK submitted data from CAL10001, a bioequivalence study, provides evidence that ABC/3TC FDC is bioequivalent to the separate components ABC 600mg + 3TC 300mg when administered as individual agents in combination with each other under fed and fasted conditions. (Please see Dr. Zheng's Biopharmaceutics Review for a detailed review). Also see Dr. Belen 's (medical officer) review of CAL10001 in appendix B of this review.

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

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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 ≤ 35 years of age.

MO Comment: *There is no obvious reason why younger subjects (namely, ≤ 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. At this time ABC/3TC FDC is recommended for adults.

MO Comment: *GSK will receive a waiver so that no data needs to be obtained on the use of ABC products in children less than three months of age. GSK is receiving a deferment regarding ABC/3TC FDC in children until PK and safety data are available on ABC OAD.*

No data on subjects with renal or hepatic impairment were submitted with this supplement. Approximately 18% of the subjects in CNA3002 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 /3TC FDC is not indicated for subjects with any degree of hepatic insufficiency.*

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I. Introduction and Background

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

ABC, a guanosine analogue, and 3TC, a cytosine analogue, are nucleoside reverse transcriptase inhibitors (NRTIs). The principle mode of action for the active moieties of ABC and 3TC is the inhibition of the HIV-1 reverse transcriptase (RT) enzyme via chain termination after incorporation of the nucleoside analogues into viral deoxyribonucleic acid (DNA). Both active ingredients, ABC and 3TC, are marketed individually under the trademarks, ZIAGEN and EPIVIR, respectively. Both products are individually approved throughout the world and indicated in combination with other antiretroviral agents for the treatment of HIV infection.

With this application GSK is seeking approval of ABC/3TC FDC (EPZICOM™). GSK expects ABC/3TC FDC as part of an ARV regimen will improve adherence. GSK proposes that ABC/3TC FDC be taken once daily with or without food and be indicated for HIV-1 infected patients in combination with other antiretrovirals, namely NNRTIs and PIs.

MO Comment: *ABC/3TC FDC should not be combined with any other NRTI in a triple nucleoside regimen. ABC/3TC FDC should not be used in conjunction with any other product that contains one or more of its components or would competitively inhibit its action (namely Epivir®, Emtricitabine®, Trizivir®, Combivir®, Ziagen®, Truvada®). This will all be highlighted in the label.*

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).

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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 once daily ABC. This application also provides indirect evidence of ABC/3TC FDC’s safety and durable efficacy.

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C. Important Milestones in Product Development

On July 21, 2003 DAVDP and GSK held a type B pre-NDA teleconference to discuss CMC data and common technical document (CTD) format of the NDA submission. Shortly thereafter on July 30, 2003 DAVDP held a face-to-face pre-NDA meeting with GSK to discuss all clinical and statistical issues. After negotiations DAVDP and GSK agreed on the data to be submitted and the format of the submission for NDA 21-652. GSK suggested and DAVDP agreed that an Advisory Committee meeting was not needed for this product.

D. Other Relevant Information

ABC/3TC FDC is not approved in any country and has not been turned down for approval in any country.

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 +

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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 animal pharmacology/toxicology provided 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. Kambhampati's Chemistry review for a detailed analysis of ABC/3TC FDC Chemistry, Manufacturing and Control of the test drug products. There were no critical CMC issues. The manufacturing and stability of the ABC/3TC FDC tablets were adequate.

Please refer to Dr. Naeger's Microbiology review for a detailed analysis of the ABC/3TC resistance data submitted with this NDA. Briefly, 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.

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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). The RT mutations emerging on therapy included M184V/I, L74V, K65R, Y115F and NNRTI-associated mutations (*i.e.*, K103N, K101X, G190S, Y181C).

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 susceptibility. 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 ~83%. 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 3.0 µg/mL.

The apparent volume of distribution after intravenous administration is approximately 0.8 L/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 CAL 10001 was a bioequivalence study of the ABC/3TC FDC tablet in fed and fasted states. Please see Dr. Zheng's review for details. The following conclusion statements are taken from Dr. Belen's medical officer review of CAL 10001:

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1. Bioequivalence between a single tablet composed of 600 mg abacavir and 300mg lamivudine versus the treatment of ZIAGEN® (abacavir) 2 x 300 mg tablet and EPIVIR® (lamivudine) 2 x 150mg tablet swallowed sequentially were demonstrated.
 2. a. 90% confidence intervals for the ratio (Treatment A : Treatment B) for the geometric LS means for AUC_{last} , AUC_{∞} , C_{max} for ABC and 3TC were in the predefined range 0.8-1.25 (table 2).
2. The plasma PK parameters t_{max} and $t_{1/2}$ for both ABC and 3TC were generally similar following administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to administration of the individual EPIVIR® and ZIAGEN® tablets.
3. In this study of thirty healthy subjects, where single fixed dose combination abacavir/lamivudine (600 mg/300mg) was compared to abacavir and lamivudine given separately, adverse reactions in the study were within the spectrum of what has been previously reported and in the current label. No abacavir hypersensitivity reactions were reported during the course of this study. No subjects withdrew from the study due to AEs.
4. For the food effect analysis, when the fixed dose combination of abacavir/lamivudine (600mg/300mg) was administered with a standard breakfast, Abacavir AUC_{last} and AUC_{∞} were similar compared to fasted state. ABC C_{max} was decreased by approximately 24% with food. Neither ABC nor 3TC had any effect by co-administration with food on $t_{1/2}$.
5. The time to peak concentration was delayed with food, and was extended by approximately one hour for both ABC and 3TC. The extent of bioavailability of abacavir was unaffected in the fed versus fasted state but the rate of bioavailability was reduced by the food effect which is similar to previous studies where ABC and 3TC were given separately.

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 7, 2004 GSK submission. The submission includes data collected from one large pivotal clinical trial (Study CNA30021) and one supportive PK study (CAL10001).

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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							
CAL10001 single US site	OL, Rand, 3 way crossover in healthy volunteers	Single dose ABC/3TC FDC tablet and single dose 600mg ABC +300mg 3TC	ABC 300 mg Sulf tab + 3TC 300mg tab or ABC/3TC FDC tablet	30	30	3 days (n=25), 2 days (n=1), 1 day (n=4)	18-50 (26) 87/13 3/73/24

¹ADC: 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

²3TC: 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/r: indinavir plus ritonavir, NFV: nelfinavir, NNRTI: non-nucleoside reverse transcriptase inhibitor, NVP: nevirapine, pbo: placebo, PI: protease inhibitors, r: ritonavir, TDF: tenofovir disoproxil fumarate, TZV: TRIZIVIR, abacavir 300mg, lamivudine 150mg and zidovudine 300mg, ZDV: zidovudine

³Medications dosed at standard, approved doses unless otherwise noted.

⁴Cap: caplets, Soln: oral solution, Succ: Succinate, Sulf: Sulfate, Tab: Tablets

⁵ABC once daily dose is 600mg; 3TC once daily dose is 300mg.

⁶Unless otherwise noted, indicates intended length of study.

C. Postmarketing Experience

ABC/3TC FDC is not yet approved in this country or in any other country, therefore, there are no postmarketing data available. Please refer to the Clinical Reviews of sNDA 20-977/S-11 and 20-978/S-12 and sNDA 20-564/S-15 for a summary of the postmarketing experience with the currently approved dose forms of ABC 300 mg BID and 3TC 300mg once daily respectively.

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

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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 NDA.

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 CAL10001 was reviewed by Dr. Belen (Medical Officer) in detail with a focus on safety. These results are incorporated into the conclusions 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 NDA, 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 NDA 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. Nicholas 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.

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Weinberg. Drs Bellos and Lang were found to be in compliance with Good Clinical Practices (GCP). Overall, DSI found no major deficiencies 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 NDA, namely CNA30021 and CAL10001 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 [redacted] as follows:

[redacted] (investigator [redacted]) at center [redacted] enrolled [redacted] patients enrolled in [redacted]. The primary efficacy analysis was performed post-hoc on the ITT population excluding these subjects from this center [redacted] 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 [redacted] 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 [redacted] had a proprietary interest in the tested product.

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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.

Based on available financial data, the \$50,000 threshold was exceeded in the case of two investigators in study [] (investigator [] at center [] enrolled 1 patient and Dr. R. Henry Dretler (investigator [] at center [] enrolled [] patients for a total of [] patients enrolled in []

GSK performed the primary efficacy analysis post-hoc on the ITT population excluding these subjects from these centers [] 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 [] centers indicated that there were no differences in measures or conclusions of the study.

***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 CAL10001 is a bioequivalence PK study, which did not contribute any information to the efficacy of the investigational product.

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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 of ART-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

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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 by determining the proportion of subjects with plasma HIV-1 RNA ≤ 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 ≤ 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

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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 decrease 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.

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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

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- 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

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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.

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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.

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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.

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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).*

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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				
Total	247/384 (64%)	252/386 (65%)	-1.0	-7.7, 5.8

***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).

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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	ABC BID
	N=384	N=386
	n (%) Responder	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	ABC BID
	N=384	N=386
	n (%)	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%)

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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%)

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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 increased 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.

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Table 13 Summary of CD4+ Cell Counts (cells/mm³) and Change from Baseline (ITT-Exposed Population, Observed - CNA30021)

Study Week	n	ABC OAD N=384		n	ABC BID N=386	
		Median (cells/mm ³)	Change from Baseline		Median (cells/mm ³)	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 present 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.

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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 ABC OAD	Screening CDC Classification	Disease Progression CDC Classification	Clinical Event
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).

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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.

Regimens including only nucleotide/nucleoside antiretroviral agents are only recommended as alternative therapy when NNRTIs and PIs cannot be used because of a disproportionate amount of virologic failures seen with triple nucleos(t)ide regimens. ABC/3TC FDC will have a usage statement to advise against using it with another NRTI alone (namely a triple nucleos(t)ide regimen).

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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

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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

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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 Dictionary 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.

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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 antiretroviral 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 $\geq 10\%$ 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.

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MO Comment: After merging like MedDRA terms fatigue + malaise, the difference between the OAD and BID arms was minimized.

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	ABC BID
	N=384 n (%)	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)

Adverse Event	ABC OAD	ABC BID
	N=384 n (%)	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/Depressed Mood	27 (7%)	27 (7%)
Headache/Migraine NOS	25 (7%)	23 (6%)
Fatigue/Malaise	22 (6%)	31 (8%)

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	ABC OAD	ABC BID
	N=384	N=386
Adverse Event	n (%)	n (%)
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 antiretroviral 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.*

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

	ABC OAD N=384	ABC BID N=386
Severe (Grade 3 and 4) Adverse Events	n (%)	n (%)
Subjects with ANY Grade 3/4 AE	101 (26%)	86 (22%)
Drug hypersensitivity	19 (5%)	8 (2%)
Increased creatine phosphokinase	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

	ABC OAD N=384	ABC BID N=386
Severe (Grade 3 and 4) Adverse Events	n (%)	n (%)
Subjects with ANY Grade 3/4 AE	101 (26%)	86 (22%)
Drug hypersensitivity	19 (5%)	7 (2%)
Increased creatine phosphokinase	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).

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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)

	Subject Number	ABC OAD N=384 n (%)	ABC BID N=386 n (%)
Fatal Adverse Events			
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

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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

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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 fatality" 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)

	ABC OAD N=384	ABC BID N=386
Serious Adverse Event	n (%)	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

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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)

	ABC OAD N=384	ABC BID N=386
Adverse Event Leading to Study Drug Discontinuation	n (%)	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))

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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	ABC BID
	N=384	N=386
	n (%)	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, headache, nausea, and abdominal pain. Table 29 provides a summary of symptoms reported by subjects with suspected ABC HSR.

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

Symptoms Reported	ABC OAD	ABC BID
	N=36 n (%)	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%)
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 symptoms 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*

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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

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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 [redacted] 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 [redacted].
- 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 [redacted]. The investigational site was not informed about the pregnancy until [redacted] at which time a positive 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

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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 [] and she stopped treatment with the investigational products on [] The subject was withdrawn from the study. The estimated date of delivery was [] 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 []
- 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 hypersensitivity reaction. She was subsequently started on stavudine (d4T, Zerit *f*) 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 [] 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 [] treatment with the investigational products was discontinued. On [] 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 [] 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

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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 [—] 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 [—] Follow up was received which specified that the subject had elected to terminate her pregnancy in (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 [—] 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 [—] 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 — grams, length — cm, cephalic perimeter of — cm, Apgar score — and Silverman score was — 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 [—] 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

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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

Chemistry Parameters	ABC OAD + 3TC + EFV		ABC BID + 3TC + EFV	
	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

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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

Hematology Parameters	ABC (OAD) + 3TC + EFV		ABC (BID) + 3TC + EFV	
	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
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%)

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	ABC OAD N=384		ABC BID N=386		
		n (%)		n (%)	
Grades 3 and 4					
Neutrophils absolute	6 (2%)	3 (<1%)	9 (2%)	4 (1%)	1 (<1%)
Platelets	2 (<1%)	0	2 (<1%)	2 (<1%)	0
WBC	0	0	0	1 (<1%)	0

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.*

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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.

DAVDP consulted the Division of Drug Risk Evaluation (DDRE) to propose a Risk Management Program (RMP) in anticipation of the introduction of a new fixed-dose formulation containing ABC. DAVDP's specific concerns revolve around ABC HSR and the risk of rechallenge with the introduction of a new ABC containing product and the increased severity of ABC HSR associated with OAD dosing. DDRE recommendations for additional risk management included educational efforts targeted to all physicians who have written at least one prescription, limitations on product sampling, enhanced passive surveillance, and the use of a physician/patient agreement. DDRE suggested that there should also be greater promotion or encouragement to all healthcare providers to report reactions to the HSR registry (please see DDRE consult for details.)

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VIII. Dosing, Regimen, and Administration Issues

GSK is recommending a new fixed dose combination of ABC 600mg/3TC 300mg to be dosed once daily with or without food. GSK submitted data from CNA30021 to establish the non-inferiority of ABC 600mg OAD compared to the adult approved dose of ABC 300mg BID. In addition GSK submitted a PK bioequivalence study, CAL10001, designed to demonstrate the bioequivalence between ABC/3TC (600mg/300mg) combination tablet versus ABC (2 x 300mg tablets) and 3TC (2 x 150mg tablets) (see Appendix B for a detailed review of CAL10001 by Dr. Belen).

ABC/3TC FDC 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-emergent 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 the median age, 35 years, as a cutoff. 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 (≤ 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.”

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MO Comment: *There is no obvious reason why younger subjects (namely, ≤ 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/m² versus 3TC 4 mg/kg twice daily + ZDV 180 mg/m². 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.

GSK recently conducted a PK study, PENTA 13, in children 2 years to < 13 years old comparing ABC OAD to ABC BID. The results of that study have not yet been submitted to DAVDP for review.

MO Comment: *GSK will receive a waiver so that no data needs to be obtained on the use of ABC products in children less than three months of age. Since ABC BID is labeled for children 3 months of age and older, GSK will need to provide PK and safety data on their ABC OAD dosing regimen for children 3 months to 17 years of age. ABC/3TC FDC is currently not recommended for children.*

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.

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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 ABC/3TC FDC. The pivotal study CNA30021 provides evidence of ABC OAD non-inferiority to ABC BID in HIV-1 antiretroviral naïve subjects and CAL10001 provides evidence of bioequivalence between ABC/3TC FDC and ABC 600mg OAD + 3TC 300mg OAD.

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 NDA can be approved. Review of the data from CNA30021 provides evidence of effectiveness and safety sufficient to support the fixed dose combination of ABC/3TC.

GSK proposed a product label that combined the most recently approved labels for ABC and 3TC with major revisions to each section of the label. After negotiations with DAVDP, GSK and DAVDP agreed upon a final label. The major revisions are described below:

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1. The DESCRIPTION section was modified to include CMC information on the ABC/3TC FDC tablet.
2. 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.
3. The CLINICAL PHARMACOLOGY section was updated to include a description of CAL10001 study results.
4. The INDICATIONS AND USAGE Section was updated to include usage statements and a description of study CNA30021 and study results in the Clinical Studies subsection, the Adverse Reactions subsection and the Laboratory Abnormalities subsection.
5. 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 CAL10001

Reviewed by: Ozlem Belen, MD

Title: An evaluation of the Bioequivalence of a Combined Formulated Tablet (600mg/300 mg abacavir lamivudine) Compared to ZIAGEN (abacavir) 2 x 300 mg Tablets and EPIVIR (lamivudine) 2 x 150mg Tablets Administered Concurrently and the Effect of Food on Absorption of the Combined Formulation in Healthy Adult Subjects

Objectives

Primary Objectives

- To demonstrate the bioequivalence between a single tablet composed of 600 mg abacavir and 300mg lamivudine versus the treatment of ZIAGEN (abacavir) 2 x 300 mg tablet and EPIVIR (lamivudine) 2 x 150mg tablet swallowed sequentially
- To evaluate the effect of food on the absorption of the new combination formulation of abacavir/lamivudine, compared to abacavir and lamivudine tablets.

Secondary Objective

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- To assess the safety and tolerability of a new combination formulation of abacavir and lamivudine.

Study Design: Study CAL10001 was a single center, open-label, randomized, three-way crossover, bioequivalence study conducted in 30 healthy volunteers. Screening took place within thirty days of the first dosing period in an outpatient setting. All subjects completing screening were allocated to receive one of the three treatments, at each period in a randomized, balanced fashion.

Subjects received the ABC/3TC FDC tablet in the fasted state, the same dose amounts of ABC and 3TC as the marketed **ZIAGEN** tablet (2 x 300mg) and **EPIVIR** tablet (2 x 150mg) in the fasted state and a third treatment consisting of the ABC/3TC FDC tablet administered with a high-fat meal.

Sequence	Sample	Period 1	Period 2	Period 3
1	5	A	B	C
2	5	B	C	A
3	5	C	A	B
4	5	A	C	B
5	5	B	A	C
6	5	C	B	A

Treatment A = Fixed dose combination of abacavir/lamivudine (600 mg/300mg) following an overnight fast

Treatment B = ZIAGEN (abacavir) 2 x 300 mg tablet and EPIVIR (lamivudine) 2 x 150mg tablet

Treatment C = Fixed dose combination of abacavir five minutes following a standardized breakfast

The study had a screening visit, three treatment visits, and a follow-up visit. The screening visit to determine enrollment eligibility was conducted within 30 days prior to receiving the first dose. For each of the three treatment visits, subjects checked-in to the study center on the day prior to dosing or Day 1. Prior to dosing on Day 1 and 24 hours following each day dosing (Day 2), the subject underwent safety assessments and PK sampling. There was a washout period of 5 to 10 days between each dose. Subjects returned to the study center for a follow-up visit within 5 to 10 days after completing the last treatment assessments or withdrawing from the study.

PK Sampling Schedule

Human plasma samples were assayed for abacavir and lamivudine using HPLC/MS/MS analysis. The standard curve QC data indicated that the plasma assay methods for abacavir and lamivudine were accurate (please refer to Dr. Jenny Zheng's PK review).

Pre-dose: within 15 minutes in fasted subjects; within 45 minutes in fed subjects.

Post-dose: 17 samples were collected in 24 hours (0.25, 0.5, 0.75, 1, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 hours post-dose.)

Number, Demographics and Other Baseline Characteristics for Subjects

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Thirty healthy adult male and female subjects between the ages of 18 to 55 (inclusive) were enrolled into the study and they were all included in the Safety Population. Twenty-five subjects completed all dosing periods and were included in the PK Summary Population. Five subjects prematurely discontinued from the study: two due to protocol violations, two withdrew consent, and one was withdrawn at the investigator's discretion.

Out of thirty subjects enrolled in the study, 26 received treatment A, 28 received treatment B and 27 received treatment C. Overall, there were 4 females and 26 males enrolled in the study. Twenty-two were whites, 2 Asians, 1 Black, and 5 Hispanics in the study. Mean weight was 79.18 kg (range 54.3-95.1 kg) and mean age was 29 (range 18-50).

***MO Comment:** Overall the population studied is mostly comprised of males and whites. The label currently states that the pharmacokinetics of ZIAGEN with respect to gender and race has not been determined. This study does not add any new information in respect to differences in gender and race.*

Study Assessments and Procedures

Each subject completed screening visit within 30 days of dosing. The following activities occurred at screening visit:

- Vital signs
- Physical examination (at screening and follow-up)
- Electrocardiogram
- Childbearing potential (for women) and type(s) of contraception
- Medical history
- Serum pregnancy test for all women
- Urine drug screen
- HIV antibody, Hepatitis B surface antigen, Hepatitis C antibody
- Concurrent medications/compliance restrictions

The following measurements were recorded in the CRF:

- Inclusion and exclusion criteria
- Current medical conditions
- Demographics: date of birth, gender, race, body weight, height, and body mass index
- Clinical laboratory tests:
 - Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count
 - Chemistry: AST, ALT, alkaline phosphatase, GGT, LDH, CPK, glucose, albumin, total protein, total bilirubin, creatinine, uric acid, BUN, serum amylase, calcium, electrolytes, (sodium, potassium, chloride, bicarbonate), triglycerides (fasted), and cholesterol (fasted)
 - Urinalysis: dipstick for blood, protein and pH
- Adverse events assessments.

Criteria for Evaluation

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Safety assessments included adverse events, clinical laboratory evaluations, electrocardiogram, physical examinations, pregnancy testing for females, and vital signs assessments. Subjects were also monitored for the symptoms of hypersensitivity reaction to abacavir.

Pharmacokinetic assessments included the collection of serial whole blood samples over 24 hours during each of the three treatment periods for bioanalysis of plasma for ABC and 3TC concentrations.

Bioequivalence and food effects were assessed from primary PK parameters (C_{max} and AUC) for treatment comparisons.

Safety Analysis

No abacavir hypersensitivity reactions were reported during this study.

There were no clinically significant laboratory abnormalities that reported as AEs. No vital signs, ECG, or physical examination results were recorded as AEs. No serious adverse events or deaths were reported during this study. There were four grade 2 adverse events reported and two of these were evaluated as being related to study drug: the two were nausea and vomiting. The two subjects with grade 2 adverse events (thought to be not study related) had vomiting and vasovagal attack. No subjects withdrew from the study due to AEs.

The most commonly reported AEs were headache (33%), nausea (23%), lightheadedness (13%), dizziness (10%), abdominal pain (10%), and tiredness (10%). The most commonly reported drug-related adverse events were similar to overall AE profile and were headache, nausea, dizziness, lightheadedness, and tiredness.

MO Comment: Adverse reactions in the study are within the spectrum of what has been previously reported and in the current label.

Table 1. Commonly Reported Adverse Events (≥5%) by Treatment Safety Population

	Treatment A N=26		Treatment B N=28		Treatment C N=27		Total N=30	
	No.	N (%)	No.	N(%)	No.	N(%)	No.	N(%)
Any event	25	14(54%)	23	12(43%)	14	11(41%)	63	22(73%)
Headache	5	5(19%)	3	3(11%)	6	6(22%)	14	10(33%)
Nausea	3	3(12%)	4	4(14%)	1	1(4%)	8	7(23%)
Lightheaded	2	2(8%)	2	2(7%)	1	1(4%)	5	4(13%)
Dizziness	3	3(12%)	1	1(4%)	0	0	4	3(10%)
Abdominal pain	1	1(4%)	2	2(7%)	0	0	3	3(10%)
Tiredness	1	1(4%)	0	0	2	2(7%)	3	3(10%)
Oral ulceration	0	0	1	1(4%)	1	1(4%)	2	2(7%)
Colic	0	0	1	1(4%)	1	1(4%)	2	2(7%)
Dyspnea	1	1(4%)	1	1(4%)	0	0	2	2(7%)

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Vomiting	1	1(4%)	1	1(4%)	0	0	2	2(7%)
Treatment A = fixed dose combination of abacavir/lamivudine (600/300 mg) fasted; Treatment B = Ziagen (2 x 300) + EPIVIR (2 x 150 mg) fasted; Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) fed. No.: number of AEs; n= number of subjects; %: percent of subjects who experienced AEs.								

Pharmacokinetics Analysis

Table 2. Plasma Abacavir Pharmacokinetic Parameter Estimates:

PK Parameter	Geometric LS Mean *		Ratio of Geometric LS Means A/B	90% CI
	Treatment A N=25	Treatment B N=25		
Abacavir				
AUC _{last} (ug*h/mL)	14.12	14.12	1.000	0.955-1.048
AUC _∞ (ug*h/mL)	14.15	14.15	1.000	0.954-1.048
C _{max} (ug/mL)	4.68	4.94	0.96	1.855-1.048
Lamivudine				
AUC _{last} (ug*h/mL)	12.36	13.00	0.951	0.910-0.995
AUC _∞ (ug*h/mL)	12.60	13.23	0.952	0.912-0.994
C _{max} (ug/mL)	2.64	2.84	0.930	0.865-0.999
Treatment A = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted Treatment B = ZIAGEN (2x 300 mg) + EPIVIR (2 x 150mg) Fasted Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed * based on log-transformed data				

MO Comment: 90% confidence intervals for the ratio (Treatment A : Treatment B) for the geometric LS means for AUC_{last}, AUC_∞ and C_{max} for ABC and 3TC were in the predefined range 0.8-1.25.

90% confidence intervals for the ratio (Treatment C: Treatment A) for the geometric LS means for AUC_{last}, AUC_∞, C_{max} of 3TC were contained range of 0.8-1.25.

Bioequivalence was shown for both abacavir and lamivudine following co-administration of the fixed dose combination of abacavir/lamivudine (600 mg/ 300 mg) compared to sequential administration of abacavir and lamivudine.

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**Table 3. Plasma ABC and 3TC Pharmacokinetic Parameter Estimates:
Geometric Mean (95%); * t_{max} values are median (range)**

Plasma APV PK Parameter	Treatment A N = 25	Treatment B N = 25	Treatment C N = 25
Abacavir			
t_{max} (h)*	1.00 (0.50-3.00)	0.75 (0.25-3.00)	2.50 (1.00-5.00)
$t_{1/2}$ (h)	2.92 (2.67-3.19)	2.86 (2.59-3.17)	3.04 (2.79-3.31)
Lamivudine			
t_{max} (h)*	2.00 (1.00-5.00)	1.50 (0.75-4.00)	3.00 (1.00-5.00)
$t_{1/2}$ (h)	4.93 (4.63-5.26)	4.99 (4.74-5.25)	4.86 (4.57-5.17)
Treatment A = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted			
Treatment B = ZIAGEN (2x 300 mg) + EPIVIR (2 x 150mg) Fasted			
Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed			

MO Comment: Plasma PK parameters t_{max} and $t_{1/2}$ for both ABC and 3TC were generally similar following administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to that of the individual EPIVIR and ZIAGEN tablets.

Food Effect Analysis

- For the food effect analysis, when the fixed dose combination of abacavir/lamivudine (600mg/300mg) was administered with a standard breakfast, Abacavir AUC_{last} and AUC_{∞} were similar compared to fasted state. ABC C_{max} was decreased by approximately 24% with food.
- The 90% CIs for the ratio (Treatment C: Treatment A) of the geometric LS means for the AUC_{last} , AUC_{∞} , and C_{max} of 3TC were contained within the equivalence range of 0.80-1.25.
- The time to peak concentration was delayed with food, and was extended by approximately one hour for both ABC and 3TC. Neither ABC nor 3TC had any effect by co-administration with food on $t_{1/2}$ or λz .

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Table 4. Abacavir (ABC) and Lamivudine (3TC) pharmacokinetic parameters following single oral administration of the fixed dose combination of abacavir/lamivudine (600 mg/300mg) fed compared to fasted state

PK Parameter	Geometric LS Mean *		Ratio of Geometric LS Means C/A	90% CI
	Treatment A N=25	Treatment C N=25		
Abacavir				
AUC _{last} (ug*h/mL)	14.12	12.74	0.902	0.861-0.945
AUC _∞ (ug*h/mL)	14.15	12.79	0.903	0.862-0.947
C _{max} (ug/mL)	4.68	3.54	0.757	0.684-0.838
Lamivudine				
AUC _{last} (ug*h/mL)	12.36	11.89	0.962	0.920-1.006
AUC _∞ (ug*h/mL)	12.60	12.13	0.963	0.922-1.005
C _{max} (ug/mL)	2.64	2.27	0.860	0.800-0.924
Treatment A = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted Treatment B = ZIAGEN (2x 300 mg) + EPIVIR (2 x 150mg) Fasted Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed * based on log-transformed data				

MO Comment: *The extent of bioavailability of abacavir was unaffected in the fed versus fasted state but the rate of bioavailability was reduced by the food effect. The food effect results are the similar to previous studies where ABC and 3TC were given separately. Current label indicates: "ZIAGEN may be taken with or without food". The food effect analysis does not provide new information which will change the label as stated above in the dosage and indication section.*

Overall Conclusions/Comments:

- Validated assays (HPLC/MS/MS) for plasma samples for abacavir and lamivudine were used. Precision and accuracy of these assays were tested using standard curve and QC data as per PK reviewer Dr. Jenny Zheng's conclusions/review.
- Bioequivalence between a single tablet composed of 600 mg abacavir and 300mg lamivudine versus the treatment of ZIAGEN® (abacavir) 2 x 300 mg tablet and EPIVIR® (lamivudine) 2 x 150mg tablet swallowed sequentially were demonstrated.
 - 90% confidence intervals for the ratio (Treatment A : Treatment B) for the geometric LS means for AUC_{last}, AUC_∞, C_{max} for ABC and 3TC were in the predefined range 0.8-1.25 (table 2).

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3. The plasma PK parameters t_{max} and $t_{1/2}$ for both ABC and 3TC were generally similar following administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to administration of the individual EPIVIR® and ZIAGEN® tablets.
4. In this study of thirty healthy subjects, where single fixed dose combination abacavir/lamivudine (600 mg/300mg) was compared to abacavir and lamivudine given separately, adverse reactions in the study were within the spectrum of what has been previously reported and in the current label. No abacavir hypersensitivity reactions were reported during the course of this study. No subjects withdrew from the study due to AEs.
5. For the food effect analysis, when the fixed dose combination of abacavir/lamivudine (600mg/300mg) was administered with a standard breakfast, Abacavir AUC_{last} and AUC_{∞} were similar compared to fasted state. ABC C_{max} was decreased by approximately 24% with food. Neither ABC nor 3TC had any effect by co-administration with food on $t_{1/2}$.
6. The time to peak concentration was delayed with food, and was extended by approximately one hour for both ABC and 3TC. The extent of bioavailability of abacavir was unaffected in the fed versus fasted state but the rate of bioavailability was reduced by the food effect which is similar to previous studies where ABC and 3TC were given separately.

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Andrea N. James, MD
Medical Officer
DAVDP
8/2/04

Concurrence
HFD-530/DivDirector/DBirnkrant

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