Module 2.5

Clinical Overview

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ABBREVIATIONS

3TC	lamivudine **(EPIVIR†)**
AAUCMB	average area under the curve minus baseline
ABC	abacavir (**ZIAGEN†**)
ABC/3TC FDC	abacavir/lamivudine fixed dose combination
AE	adverse event (experience)
AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
AUC_{∞}	area under the plasma concentration versus time curve from time 0 and extrapolated to infinity
BID	twice daily dosing (Bis In Die)
C_{max}	Steady-state peak concentrations
$C_{max, ss}$	Steady-state peak concentrations at steady state
CBV-TP	carbovir triphosphate
CD4+	helper-inducer T-lymphocyte surface antigen
CI	Confidence Interval
CRF	case report form
CSR	clinical study report
d4T	stavudine (Zerit†)
ddI	didanosine (Videx†)
ddC	zalcitabine, (Hivid†)
EFV	efavirenz (Sustiva†or Stocrin*)
FDC	Fixed dose combination
GLS	Geometric Least Squares
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HIV-1	Human Immunodeficiency Virus Type 1
HCP	Health care professional
HSR	hypersensitivity reaction
IC_{50}	50% inhibitory concentration
ITT	Intent-to-Treat
ITT	Intent-to-Treat
NFV	nelfinavir (Viracept†)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OAD	once daily
PBMCs	peripheral blood mononuclear cells
PI	protease inhibitor
PK	pharmacokinetics
RNA	ribonucleic acid
SAE	serious adverse event
t_{max}	time of maximum concentration
TDF	tenofovir disoproxil fumarate (Viread†)
TLOVR	Time to Loss of Virologic Response
TZV	**TRIZIVIR†** (abacavir sulfate, lamivudine and zidovudine)
ZDV	zidovudine (**RETROVIR†**)

1. PRODUCT DEVELOPMENT RATIONALE

1.1. Introduction

The optimal long-term management of human immunodeficiency virus type 1 (HIV-1) infection currently necessitates the chronic use of antiretroviral therapy (ART) that is highly effective, well tolerated, and can preserve future treatment options. Poor adherence has been associated with the development of drug resistance, increased likelihood of virologic failure, and increased morbidity and mortality [Paterson, 2000; Carmona, 2000; Walsh , 2000; Panel on Clinical Practices for Treatment of HIV Infection, 2003]. There is evidence that simplified regimens with reduced pill numbers and dose frequencies improve adherence [Bartlett, 2001; Vibhagool, 2001].

Clinical data suggest that subjects receiving ART sporadically or at suboptimal doses will develop drug resistant virus over time. Moreover, development of resistance to one antiretroviral drug may produce cross-resistance to other drugs within the same class, thereby jeopardizing future treatment options. The availability of new drug formulations with simpler dosing schedules may enhance subject compliance with ART. The results of a study in which subjects had an opportunity to switch from a current triple-ART therapy to **TRIZIVIR**[†] **(**abacavir [ABC, **ZIAGEN**[†]], lamivudine [3TC, **EPIVIR**[†]] and zidovudine [ZDV, **RETROVIR**[†]**]**) administered as one tablet twice daily demonstrated an increased self-reported adherence on **TRIZIVIR** that suggests that subjects judged the simplified regimen as more convenient for long-term use [Katlama, 2003].

As discussed above, the need exists for the development of new drugs and drug formulations that are convenient and efficacious with good tolerability in both treatment naïve and experienced subjects. Although several antiretroviral drugs have been licensed for once daily administration, the number of treatment regimens that can be dosed entirely once daily is currently limited since some medications cannot be dosed together. For example, different dietary restrictions may preclude dosing certain once daily antiretroviral agents together at one time.

Towards the goal of simplifying therapy, GlaxoSmithKline (GSK) undertook a clinical development program with the aim of combining two antiretrovirals with established efficacy and safety into a fixed dose combination (FDC) product for once daily

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† **ZIAGEN** is a Trade Mark of the GlaxoSmithKline group of companies. Registered in US Patent and Trademark Office.

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administration. ABC and 3TC were identified as candidates for co-formulation as both are potent NRTIs, with established safety profiles, limited potential for drug interactions, and no dietary restrictions. In addition, this combination is associated with a low potential for mitochondrial toxicity [Kakuda, 2000] and has a favorable resistance profile [McManus, 2003].

A clinical pharmacology study (CNA10905) investigated the intracellular half-life of carbovir triphosphate (CBV-TP), the active moiety of ABC. A pivotal clinical trial (CNA30021) was conducted to provide safety, efficacy, and durability data comparing administration of ABC once daily (OAD) to ABC twice daily (BID) in combination with 3TC and efavirenz (EFV, Sustiva[†], Stocrin[*]) once daily. The pivotal bioequivalence study (CAL10001) was conducted to support the use of the ABC/3TC FDC tablet.

A tabular listing of studies discussed in this application is provided in Module 5 (m5, Section 5.2). A synopsis of each study is provided in Module 2 (m2, Section 2.7.6).

1.2. Contribution of New Product

The ABC/3TC FDC tablet provides an important therapeutic option in the management of HIV infection because for the first time, a dual NRTI backbone can be administered as one tablet once a day.

Additional attributes of the product are as follows:

- A combination of two highly active NRTIs;
- A combination of two NRTIs with acceptable safety profiles;
- Absence of fluid or dietary restrictions;
- A low potential for clinically significant drug-drug interactions;
- A combination that may be beneficial for subjects needing to simplify their treatment regimens;
- A combination that may be beneficial for subjects receiving directly observed therapy; and
- A favorable resistance profile that may preserve future treatment options.

1.3. Clinical Development Program

3TC is currently approved for once daily (300mg) and for twice daily (150mg) administration while ABC 300mg is currently approved for twice daily administration (total daily dose of 600mg). GSK has developed a FDC tablet that contains ABC 600mg

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[†] Sustiva is a Trade Mark of Bristol-Myers Squibb Company. Registered in US Patent and Trademark Office.

[*] Stocrin is a Trade Mark of Merck Company.

and 3TC 300mg (ABC/3TC) for once daily administration. The development strategy is based upon one pivotal clinical trial (CNA30021), a pivotal bioequivalence study CAL10001, and a supporting clinical pharmacology study CNA10905. Four previously submitted (NDA 20-977 S:011, 13 June, 2003) clinical trials (CNA30024, ESS40001, APV30001, and APV30002) demonstrated the utility of the ABC + 3TC NRTI backbone when combined with other classes of antiretroviral drugs.

CNA30021 confirmed the non-inferiority of ABC dosed once daily versus twice daily when administered with 3TC and EFV once daily. In addition to CNA30021, CAL10001 established the bioequivalence of the FDC tablet of ABC/3TC compared with the marketed formulations as **ZIAGEN** 2 x 300mg tablets and **EPIVIR** 2 x 150mg tablets. CNA10905 demonstrated a prolonged (>20 hours) intracellular half-life of CBV-TP which supports ABC 600mg once daily dosing.

1.4. Claimed Indications and Dosage

The ABC/3TC FDC tablet is indicated for the treatment of HIV-1 infection in combination with other ART. The recommended oral dose for the ABC/3TC FDC tablet for adults and adolescents weighing ≥40kg is one tablet administered once a day.

Because of the fixed dose nature of the ABC/3TC tablet, it is recommended that separate preparations of **ZIAGEN** and **EPIVIR** be administered when dose adjustments for one or both of the components are required.

1.5. Compliance with Good Clinical Practice

All studies were undertaken in accordance with standard operating procedures of the GSK Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the Declaration of Helsinki. Where regulatory approval was required, this was obtained from the relevant health authorities.

2. OVERVIEW OF BIOPHARMACEUTICS

Biopharmaceutical support for the ABC/3TC FDC tablet is provided by investigation of *in vitro* dissolution and by pivotal bioequivalence study CAL10001, in accordance with current regulatory guidance [CDER, 2001; CDER, 2002; CPMP, 2001; Minister of Health Canada, 1992]. Results from these investigations are briefly summarized below. Detailed result summaries are provided in the Clinical Summary of Biopharmaceutics in Module 2 (m2, Section 2.7.1).

2.1. ABC/3TC FDC Tablet Formulation and *In Vitro* Dissolution

The ABC/3TC FDC tablets have been shown to be physically and chemically stable. The formula and direct compression manufacturing process of the FDC tablet are similar to those for the marketed **ZIAGEN** and **EPIVIR** tablets.

In vitro dissolution testing demonstrated that the ABC/3TC FDC tablet batch utilized in the bioequivalency study CAL10001 met the proposed specification for dissolution of the quantity of active dissolved expressed as a percentage of the labeled content (Q).
Q = % of labeled strength within 30 minutes for both ABC and 3TC.

2.2. Bioequivalence Study CAL10001

Study CAL10001 was a single center, open-label, randomized, three-way crossover, bioequivalence study conducted in 30 healthy volunteers. 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.

Bioequivalence was established for the ABC/3TC FDC tablet compared with administration of the separate **ZIAGEN** and **EPIVIR** tablets in the fasted state. Geometric Least Squares (GLS) mean ratios and 90% confidence intervals (CI) for ABC area under the plasma concentration versus time curve from time 0 and extrapolated to infinity (AUC_∞) and peak concentrations (C_{max}) were 1.000 (0.954, 1.048) and 0.946 (0.855, 1.048), respectively. Corresponding values for 3TC were 0.952 (0.912, 0.994) and 0.930 (0.865, 0.999). These values for both ABC and 3TC are well within the bioequivalence acceptance CI range of 0.80 to 1.25.

There was no clinically significant food effect on either ABC or 3TC bioavailability from administration of the ABC/3TC FDC tablet administered with a high-fat meal compared with administration of the FDC tablet in the fasted state. GLS mean ratios and 90% CI for ABC AUC_∞ and C_{max}, fed versus fasted, were 0.903 (0.862, 0.947) and 0.757 (0.684, 0.838), respectively. Corresponding values for 3TC were 0.963 (0.922, 1.005) and 0.860 (0.800, 0.924). The time to peak concentration (t_{max}) was delayed with food and was extended by approximately 1 hour for both ABC and 3TC, which may be due to the reduced frequency of gastric emptying often seen in the fed state. These effects are similar to those historically observed for the marketed ABC and 3TC tablet formulations and are not considered to be clinically significant. The results indicate that, as with existing **ZIAGEN** and **EPIVIR** tablets, the ABC/3TC FDC tablet can be taken with or without food.

2.3. Biopharmaceutics Conclusions

- *In vitro* dissolution testing demonstrated that the ABC/3TC FDC tablet formulation meets the proposed specification for dissolution of Q = % of labeled strength within 30 minutes for both ABC and 3TC. The FDC tablet batch utilized in the bioequivalency study met the proposed specification.
- The ABC/3TC FDC tablet is bioequivalent to the marketed **ZIAGEN** and **EPIVIR** tablets.
- The ABC/3TC FDC tablet can be taken with or without food.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This section summarizes the clinical pharmacology of ABC and 3TC from historical data and results of a new clinical pharmacology study, CNA10905, which characterized the intracellular pharmacokinetics of CBV-TP. A more detailed summary of results from CNA10905 is provided in the Summary of Clinical Pharmacology Studies in Module 2 [m2, Section 2.7.2].

3.1. Summary of Abacavir and Lamivudine Clinical Pharmacology

The pharmacokinetics of ABC and 3TC have been extensively studied and well characterized. A brief synopsis of pharmacokinetic information available in the approved labeling for **ZIAGEN** and **EPIVIR** is provided for reference.

3.1.1. Abacavir

The currently recommended dosage of **ZIAGEN** (abacavir, ABC) in adults is 300mg twice daily. The recommended dose for adolescents and pediatric patients 3 months to 16 years of age is 8mg/kg twice daily, up to a maximum of 300mg twice daily.

ABC is rapidly and well absorbed after oral administration. Peak concentrations typically occur about 1 to 2 hours after dosing and the absolute bioavailability of ABC is approximately 83%. ABC pharmacokinetics are linear and dose-proportional over the range of 300 to 1200mg/day. After oral administration of a single dose of 600mg of ABC in 20 patients, C_{max} was 4.26 ± 1.19 µg/mL (mean ± standard deviation [SD]) and AUC_{∞} was 11.95 ± 2.51 µg•hr/mL (CNAA2001). Steady-state peak concentrations ($C_{max, ss}$) from 300mg twice daily dosing are approximately 3.0 ± 0.9 µg/mL (mean ± SD). Coadministration with food has no significant effect on ABC bioavailability; therefore, ABC may be administered with or without food (Study CNAA1009).

The apparent volume of distribution of ABC after intravenous administration is 0.86 ± 0.15L/kg. Binding to plasma proteins is moderate at about 50% and is independent of concentration.

ABC is extensively metabolized by the liver with less than 2% excreted as unchanged drug in the urine. It is primarily metabolized via two pathways, uridine diphospho-glucuronyl transferase and alcohol dehydrogenase, resulting in the inactive glucuronide metabolite (361W94, ~ 36% of the dose recovered in the urine) and the inactive carboxylate metabolite (2269W93, ~ 30% of the dose recovered in the urine). The remaining 15% of ABC equivalents found in the urine are minor metabolites, each representing less than 2% of the total dose. Fecal elimination accounts for about 16% of the dose. The terminal elimination plasma half-life of ABC is approximately 1.5 hours.

There are limited data for ABC in subjects with renal dysfunction or hepatic impairment. ABC pharmacokinetics have been studied in six HIV-infected subjects with end stage renal disease. No changes were observed in ABC pharmacokinetics compared with

healthy adults. This is consistent with the kidney being a minor route of ABC elimination. A study of ABC pharmacokinetics in subjects with hepatic impairment (Study CNAB1006) suggested that the ABC daily dose should be reduced in subjects with mild hepatic impairment (Child-Pugh score of 5-6) and contraindicated in patients with moderate to severe hepatic impairment due to altered ABC pharmacokinetics. The ABC/3TC FDC will not be proposed for use in patients with mild hepatic impairment as dose reduction of ABC is recommended.

3.1.2. Lamivudine

The recommended dose for **EPIVIR** (lamivudine, 3TC) in adults is 300mg daily, administered as either 300mg once daily or 150mg twice daily. The recommended dose for pediatric subjects up to 16 years of age is 4mg/kg twice daily, up to a maximum of 150mg twice daily.

3TC is rapidly absorbed after oral administration. Absolute bioavailability is approximately 86% of the administered dose. Over the oral dose range of 0.25 to 10mg/kg, 3TC AUC and C_{max} increase in proportion to dose. Mean (±SD) steady-state peak concentrations of approximately 1.5 ± 0.5 µg/mL are obtained from 2mg/kg twice daily dosing and occur at about 1 to 1.5 hours after administration. After multiple-dose oral administration of 3TC 300mg once daily for 7 days to 60 healthy volunteers, steady-state C_{max} was 2.04 ± 0.54 µg/mL (mean ± SD) and the 24-hour AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 µg•hr/mL. When administered with food, the rate of 3TC absorption is reduced (~ 2 hour delay in t_{max} and ~ 40% reduction in C_{max}). However, there is no significant difference in systemic exposure (AUC_{∞}) between the fed and fasted states; therefore, 3TC may be administered with or without food.

After intravenous administration, the apparent volume of distribution is independent of dose and is 1.3 ± 0.4 L/kg, suggesting extravascular distribution. Binding of 3TC to human plasma proteins is low (<36%).

The observed mean elimination serum half-life of 3TC ranged from 5 to 7 hours in healthy adults, HIV-infected subjects, or HBV-infected subjects. The majority of 3TC, approximately 70%, is eliminated unchanged in urine. Renal clearance (0.22 L/h/kg following a single intravenous dose) exceeds the glomerular filtration rate, indicating active tubular secretion by the kidneys. Oral clearance is approximately 0.37 L/h/kg. Non-renal elimination accounts for the remainder of 3TC elimination. In man, the only known metabolite of 3TC is the trans-sulfoxide metabolite; approximately 5% of a dose is excreted in the urine as this metabolite. 3TC pharmacokinetics in adults are not altered by diminished hepatic function; dosage adjustment is not required in subjects with hepatic impairment. Dosage reduction is recommended in renally impaired subjects (creatinine clearance <50mL/min) and therefore the ABC/3TC FDC will not be proposed for use in renally impaired subjects.

3.1.3. Drug Interactions

In humans, ABC and 3TC are not significantly metabolized by cytochrome P450 enzymes; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

A clinically significant drug interaction between ABC and 3TC has not been observed; this is probably attributable to their different elimination pathways. Although ABC and ZDV share common metabolic pathways via glucuronyl transferase, no clinically relevant changes in the pharmacokinetics of ABC or ZDV have been observed with concurrent administration (Study CNA1002).

Coadministration of ethanol and ABC in male subjects resulted in a clinically insignificant increase in ABC AUC_{∞} and the apparent plasma half-life (Study CNAA1010). ABC had no effect on the PK properties of ethanol. Although this interaction has not been studied in females, no clinically significant interaction is expected between ABC and ethanol. HIV-infected subjects receiving methadone-maintenance therapy (40mg and 90mg daily) with 600mg of **ZIAGEN** twice daily (twice the recommended daily dose for ABC) may experience increased methadone clearance which may require an increased methadone dose (Study CNAA1012).

3TC is not recommended for co-administration with zalcitabine (ddC, Hivid[†]) due to mutual inhibition of intracellular phosphorylation. Renal elimination of 3TC is inhibited by trimethoprim which results in an increase in 3TC AUC of ~ 40%; however, no dosing adjustment is required. There is no other known clinically relevant drug interaction for 3TC.

ESS30009 is a randomized (1:1), open-label, multicenter study that was designed to evaluate the safety and durability of EFV + ABC/3TC once daily versus tenofovir (TDF, Viread[†]) + ABC/3TC once daily over 48 weeks in approximately 306 ART-naive subjects. Shortly after initiation of this study, reports of poor virologic response in subjects receiving TDF + ABC/3TCwere observed. Results from an expedited unplanned analysis showed a poor virologic response in the TDF + ABC/3TC group as compared to the EFV + ABC/3TC group. Based on the preliminary results, the TDF + ABC/3TC treatment group of this study was recently terminated. The nature of any interaction between the components of this regimen is being investigated. Preliminary study results indicate that ABC/3TC should not be used with TDF as part of triple antiretroviral therapy.

No new drug interactions are expected with the ABC/3TC FDC.

[†] Hivid is a Trade Mark of Roche.
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[†] Viread is a Trade Mark of the Gilead Sciences Inc.
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3.2. Clinical Pharmacology Support for Once-Daily Dosing

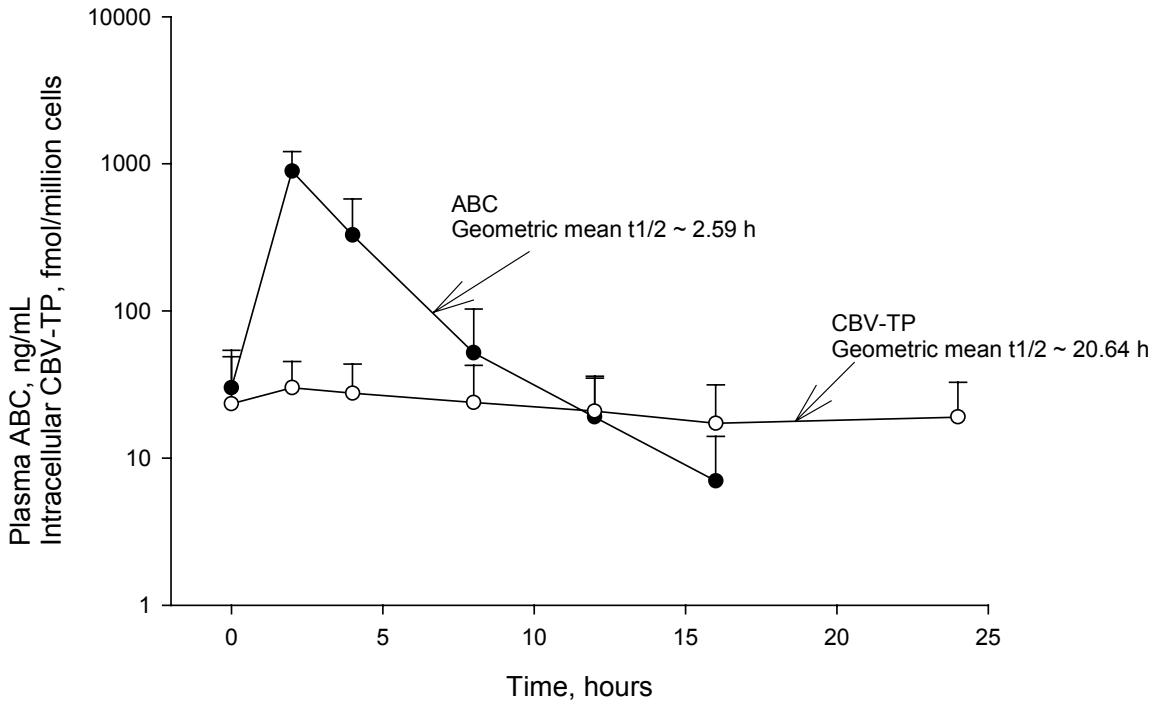
3.2.1. Background

3TC is approved for once or twice daily dosing. Currently, the standard dosing regimen of ABC for the treatment of HIV infection is 300mg administered twice daily. Preclinical and clinical data suggested that once daily administration of ABC might also be possible [Bilello, 1997; Drusano, 2002], due to a long (>12 hours) intracellular half-life of CBV-TP [Kewn, 2000; Harris, 2002]. A clinical pharmacology study, CNA10905, was conducted by GSK to further investigate the intracellular PK of CBV-TP, using a validated assay, consistent with Good Laboratory Practice. Results from study CNA10905 are briefly discussed below. A detailed summary of PK parameters from plasma ABC and intracellular CBV-TP are provided in Module 2 (m2, Section 2.7.2).

3.2.2. Clinical Pharmacology Study CNA10905

Study CNA10905 was an open-label, single arm, pilot study in 20 HIV-infected subjects. The subjects were on a stable ABC 300mg twice daily containing regimen (as either **ZIAGEN** or **TRIZIVIR**) for at least 6 weeks. The intracellular PK of CBV-TP at steady-state in peripheral blood mononuclear cells (PBMCs) were determined over a 24-hour interval, with the second dose withheld on the PK sampling day. Results from this study were generally consistent with the previous findings for ABC plasma PK as well as prolonged intracellular CBV-TP elimination [Kewn, 2000; Harris, 2002]. The concentration-time profiles for plasma ABC and intracellular CBV-TP observed in study CNA10905 are illustrated in Figure 1.

Figure 1 CNA10905: Mean (SD) Concentration versus Time Profiles of Plasma ABC and Intracellular CBV-TP



Note: Blood samples were collected up to 24 hours post dose at steady state with the second dose on the same day skipped.
Source data: Table 12.3 and Table 12.5 of Study CNA10905

The intracellular CBV-TP concentration-time profiles demonstrated a generally flat terminal elimination phase with a prolonged geometric mean terminal half-life of 20.64 hours (95% CI: 16.39, 25.99 hours). CBV-TP concentrations in the previously published reports [Kewn, 2000; Harris, 2002] were somewhat higher than those observed in CNA10905. The CBV-TP concentration differences are likely related to differences in assay methodology. CNA10905 used whereas that used by Kewn and Harris was a less specific nucleotide enzymatic substitution assay. The intracellular CBV-TP concentrations in CNA10905 still averaged about 2-fold greater than the reported inhibition constant (Ki) value of 21nmol/L [Daluge , 1997] for inhibition of 2-deoxyguanosine-5`-triphosphate (dGTP) incorporation into DNA by HIV-1 reverse transcriptase throughout the 24 hour sampling period (50 fmol/10^6 cells of CBV-TP = 100 nmol/L).

The short plasma half-life of ABC along with a long terminal half-life of intracellular CBV-TP in PBMCs suggest that there is a pooling of one of the precursors of CBV-TP (e.g., abacavir monophosphate, carbovir monophosphate or carbovir diphosphate) within the cell. Although study CNA10905 investigated the PK of a single 300mg dose of ABC over 24 hours in subjects at steady state on a twice daily regimen, similar intracellular kinetics for CBV-TP are expected from ABC 600mg once daily due to the likely pooling mechanism of one of the precursors of CBV-TP inside the cell. Importantly, the efficacy of ABC 600mg once daily dosing was demonstrated in pivotal efficacy study CNA30021

included in this submission, which confirmed the non-inferiority of the ABC 600mg once daily regimen versus 300mg twice daily (Section 4).

3.3. Clinical Pharmacology Conclusions

- A prolonged geometric mean intracellular CBV-TP half-life of approximately 20 hours was observed in clinical pharmacology study CNA10905. This is consistent with two prior independent studies and supports ABC 600mg once daily dosing as an effective component of antiretroviral therapy and the use of the proposed ABC/3TC FDC tablet in the treatment of HIV-infected patients.
- Because of the fixed dose nature of the ABC/3TC FDC tablet, it is recommended that separate preparations of **ZIAGEN** and **EPIVIR** be administered when dose adjustments of ABC are necessary due to hepatic impairment, when adjustments of 3TC are necessary due to renal impairment (creatinine clearance ≤50 mL/min), and for use of either ABC and/or 3TC in adolescents <40 kg.

4. OVERVIEW OF EFFICACY

The efficacy of the separate components of the ABC/3TC FDC tablet is well established and was demonstrated in the respective **ZIAGEN** and **EPIVIR** NDA submissions. 3TC is currently approved for twice daily (150mg) and for once daily administration (300mg) and ABC 300mg tablets are currently approved for twice daily administration (total daily dose of 600mg).

Establishing the efficacy of the ABC/3TC FDC tablet for once daily administration therefore has two key components;

- demonstrate that the ABC/3TC FDC tablet is bioequivalent to the separate components;
- demonstrate that ABC 600mg once daily is non-inferior to ABC 300mg given twice daily.

As previously discussed in the Biopharmaceutics and Clinical Pharmacology Overview of this document (Section 2 and Section 3), the pharmacokinetic study CNA10905 supports once daily dosing of ABC and the pivotal bioequivalence study CAL10001 demonstrated that the ABC/3TC FDC tablet is bioequivalent to the separate components.

CNA30021 is considered the pivotal clinical efficacy trial for the application and demonstrated the non-inferiority of ABC 600mg once daily to ABC 300mg twice daily in combination with 3TC and EFV (Table 1).

A detailed discussion of the efficacy data provided in this application is included in the Clinical Summary of Efficacy in Module 2 (m2, Section 2.7.3).

Table 1 Description of the Clinical Efficacy and Safety Study

Protocol Number	Treatment Groups Abbreviation[1]	Treatment Received	Population	No. Subjects Randomized / Treated	Treatment Duration
Pivotal Study					
CNA30021	ABC once daily	ABC 600mg OAD + ABC 0 mg BID + 3TC 300mg OAD + EFV 600mg OAD	ART- Naïve CD4+ >50 cells/mm^3 HIV-1 RNA >400 copies/mL	392 / 384	48 weeks
	ABC twice daily	ABC 300mg BID + ABC 0 mg OAD + 3TC 300mg OAD + EFV 600mg OAD		392 / 386	

1. OAD: once a day; BID: twice a day.

4.1. Clinical Trial Methodology and Design

The pivotal study CNA30021 was a Phase III, randomized, double-blind, multicenter, international study designed to evaluate the antiretroviral 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.

Efficacy endpoints chosen for study CNA30021 are considered current standards by which to determine efficacy of ART in HIV-infected subjects. In ART-naïve subjects, the ability of a treatment regimen to produce maximal and durable plasma HIV-1 ribonucleic acid (RNA) suppression (reducing plasma HIV-1 RNA below the lower limit of quantitation of the assay) is an appropriate test to compare treatment groups. As such, the proportion of subjects achieving a plasma HIV-1 RNA threshold of 50 copies/mL (or 400 copies/mL), based on the time to loss of virologic response (TLOVR) algorithm was evaluated over 48 weeks. The TLOVR algorithm is a conservative approach that depends not only on plasma HIV-1 RNA data, but is a composite of the plasma HIV-1 RNA data in conjunction with other data such as treatment discontinuations for any reason, other antiretroviral drug additions and/or clinical disease progression data.

The primary efficacy measure to test the non-inferiority of ABC once daily versus ABC twice daily was the comparison of the proportion of subjects with plasma HIV-1 RNA levels <50 copies/mL through Week 48. Data were summarized and plotted by week on the Intent-to-Treat (ITT)-Exposed Population, which included all subjects randomized and exposed to at least one dose of study drug. An As-treated population was also employed which was a subset of the ITT-Exposed Population and only included data collected from subjects while on randomized study drug. The test of the hypothesis of non-inferiority was based on the calculation of a two-sided 95% CI on the point estimate of the treatment difference in the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 using the Cochran Mantel Haenszel method stratified by baseline plasma HIV-1 RNA (≤100,000 copies/mL; >100,000 copies/mL).

Secondary efficacy endpoints included:

- comparison of the proportion of subjects with plasma HIV-1 RNA levels <50 copies/mL at Week 48 (As-Treated Population);
- comparison of the proportion of subjects with plasma HIV-1 RNA levels <400 copies/mL at Week 48 (ITT-Exposed Population);
- comparison of the time to treatment failure using the TLOVR algorithim;
- cumulative antiviral efficacy (plasma HIV-1 RNA - absolute change from baseline and time-weighted decrease, defined as the average area under the curve minus baseline [AAUCMB]); and
- immunologic efficacy (CD4+ cell count - absolute change from baseline and time-weighted increase [AAUCMB]).

These secondary efficacy endpoints are also well established as surrogate markers and are appropriate for assessing and comparing the efficacy of antiretroviral therapy.

4.1.1. Statistical Methods

The surrogate marker changes were summarized by the percentage of subjects with plasma HIV-1 RNA levels below a pre-defined limit. Treatment groups were compared using the Cochran Mantel Haenszel test controlling for randomization strata. The durability of the plasma HIV-1 RNA response was assessed in a time from first dose to a plasma HIV-1 RNA event analysis (Kaplan-Meier). The TLOVR algorithm is a conservative approach that depends not only on HIV-1 RNA data, but is a composite of the RNA data in conjunction with other data such as treatment discontinuations for any reason, other antiretroviral drug additions, and/or clinical disease progression data.

Two-sided tests of significance, at the alpha level of 0.05 were used throughout the analyses.

The sample size in pivotal study CNA30021 was based on 90% power to assess a non-inferiority margin of 12% at the 0.05 level of significance. The non-inferiority margin of 12% was pre-selected as the appropriate measure for distinguishing the clinical effectiveness of two study treatments. The choice of delta was based largely on expert clinical judgement and discussion with independent HIV physicians, with 12% representing the largest difference that would be clinically acceptable. Furthermore, to exclude 12% from the CI with this sample size and this assumed success rate, the observed virologic response rates would need to differ by no more than 4% to 5%, a difference considered to be clinically unimportant. The active control in this study of ABC twice daily + 3TC + EFV was established in the previously submitted study CNA30024 as non-inferior to a widely used and widely recommended first-line treatment of ZDV + 3TC + EFV (GlaxoSmithKline Document Number RM2002/00225/00).

4.2. Efficacy Assessment of Pivotal Study CNA30021

Use of ABC once daily compared with twice daily in combination with 3TC and EFV once daily in treatment-naïve HIV-1 infected adults

The pivotal study CNA30021 was a Phase III, 1:1 randomized, double-blind, multicenter international study of 770 ART naïve, HIV-1 infected subjects over at least 48 weeks duration. Subjects were randomized to receive ABC 600mg once daily or ABC 300mg twice daily, as a component of highly active antiretroviral therapy (HAART) along with 3TC 300mg once daily and EFV 600mg once daily.

The median baseline HIV-1 RNA level and CD4+ cell count were 4.9 $\log_{10}$ copies/mL and 262 cells/mm^3, respectively, in this subject population and balanced between the treatment groups.

A summary of treatment outcomes at Week 48 (based on TLOVR) for the ITT-Exposed population with plasma HIV-1 RNA <50 copies/mL and <400 copies/mL is presented in Table 2.

Table 2 Summary of Treatment Outcomes at Week 48 using the TLOVR algorithm for Plasma HIV-1 RNA <50 copies/mL and <400 copies/mL (ITT-Exposed Population - CNA30021)

Outcome	ABC OAD N= 384		ABC BID N= 386	
	<50 copies/mL, n (%)	<400 copies/mL, n (%)	<50 copies/mL, n (%)	<400 copies/mL, n (%)
Responder	253 (66%)	276 (72%)	261 (68%)	279 (72%)
Virologic Failure	38 (10%)	15 (4%)	32 (8%)	16 (4%)
Rebound	9 (2%)	10 (3%)	8 (2%)	12 (3%)
Never suppressed through Week 48	27 (7%)	3 (<1%)	21 (5%)	2 (<1%)
Insufficient plasma HIV-1 RNA response[1]	2 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)
Discontinued or changed therapy due to AE	50 (13%)	50 (13%)	42 (11%)	42 (11%)
Discontinued or changed therapy due to other reasons	43 (11%)	43 (11%)	51 (13%)	49 (13%)
Consent withdrawn	10 (3%)	10 (3%)	10 (3%)	10 (3%)
Lost to follow-up	20 (5%)	20 (5%)	23 (6%)	22 (6%)
Protocol violation	1 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Insufficient CD4+ Response	0	0	0	0
Clinical progression	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Change of ART[2]	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
Other	9 (2%)	9 (2%)	14 (4%)	13 (3%)

Source Data: Table 13.5 and Table 13.50 of the CNA30021 Clinical Study Report (CSR).
1. As recorded on the treatment discontinuation Case Report Form (CRF) page
2. Excluding changes to background medications (3TC and EFV)

The tabulations within a given category may differ between the 50-copy and 400-copy thresholds. In general, the TLOVR algorithm classifies a subject as a responder at the time of 2 consecutive measurements below the threshold; the subject then remains classified as a responder until a confirmed loss of suppression (i.e., a rebound) or a premature treatment discontinuation. If the premature treatment discontinuation occurs before the rebound, then the failure is classified according to the reason for discontinuation as listed in Table 2. For example, Subject 01* was a virologic success according to the 400-copy threshold, but subsequently had a rebound. The subject was lost to follow up before achieving 2 plasma HIV-1 RNA measurements below 50 copies/mL. Consequently, the failure at Week 36 is classified as "Lost to follow-up" with the 50-copy threshold and "Rebound" with the 400-copy threshold.

Virologic failure rates were low and similar between treatment groups. Withdrawals/discontinuations, when they occurred, were most likely due to an adverse event (AE) among subjects in either treatment group (11% to 13%). Eleven percent (43/384) of subjects in the ABC once daily group and 13% (51/386) of subjects in the ABC twice daily group discontinued treatment due to other reasons. Overall, there were no apparent treatment-related trends in reasons for treatment discontinuation.

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The proportions of subjects in CNA30021 who prematurely discontinued for any non-virologic reason by Week 48 (ABC once daily, 24%; ABC twice daily, 24%) were comparable to other GSK-conducted studies with similar study designs and treatment duration (EPV20001, CNA30024, APV30001, and APV30002) and not attributable to any specific drug, dosing schedule or treatment regimen (Table 3).

Table 3 Summary of Premature Discontinuations Across Studies

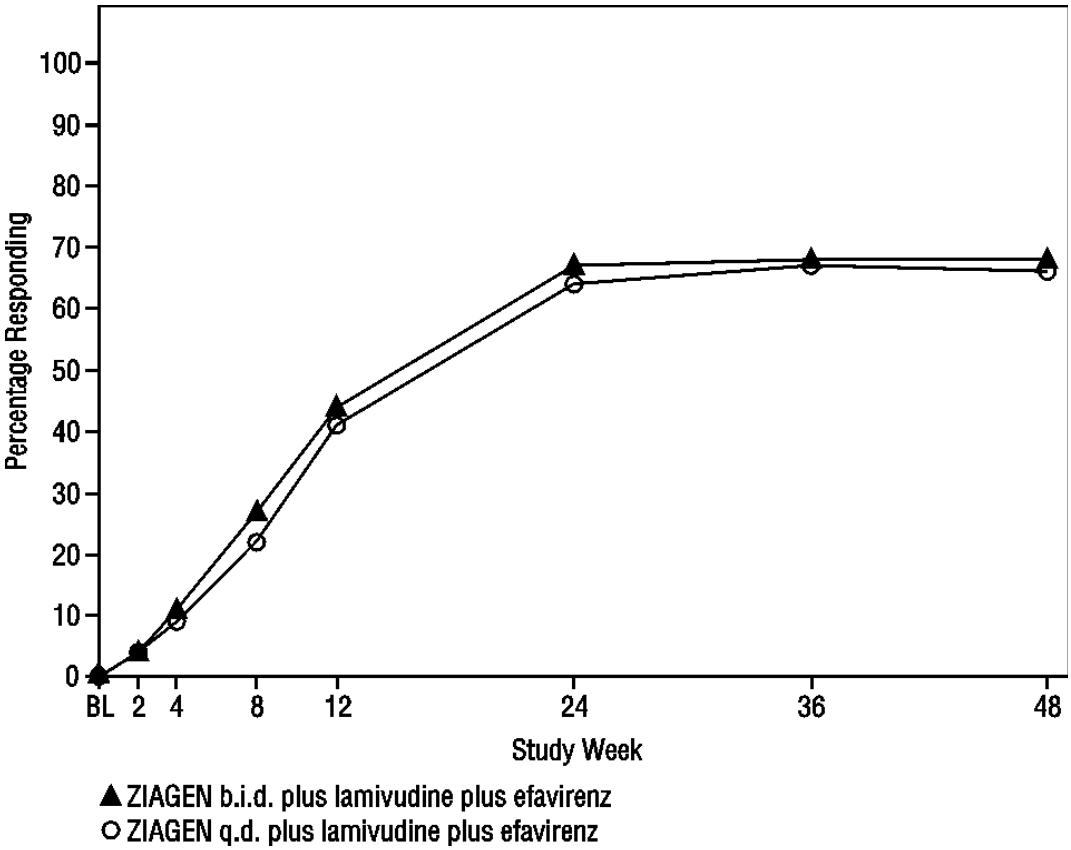
Study	Incidence of Discontinuations by Treatment Group	
EPV20001	3TC OAD + ZDV + EFV: 24%	3TC BID + ZDV + EFV: 26%
CNA30024	ABC + 3TC + EFV: 24%	ZDV + 3TC + EFV: 27%
APV30001	ABC + 3TC + 908: 23%	ABC + 3TC + NFV: 27%
APV30002	ABC + 3TC + 908/RTV: 28%	ABC + 3TC + NFV: 18%

Source Data: Table 9 of the EPV20001 CSR, Table 9 of the CNA30024 CSR, Table 1 of the APV30001 CSR, and Table 1 of APV30002 CSR; NFV=nelfinavir (Viracept†).

Figure 2 presents the ITT-Exposed, TLOVR analysis of proportions of subjects with plasma HIV-1 RNA <50 copies/mL through Week 48.

† Viracept is a Trade Mark of Agouron Pharmaceuticals Inc., a Pfizer company. Registered in US Patent and Trademark Office.

Figure 2 Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL by Study Week using the TLOVR Algorithm (ITT-Exposed Population - CNA30021)

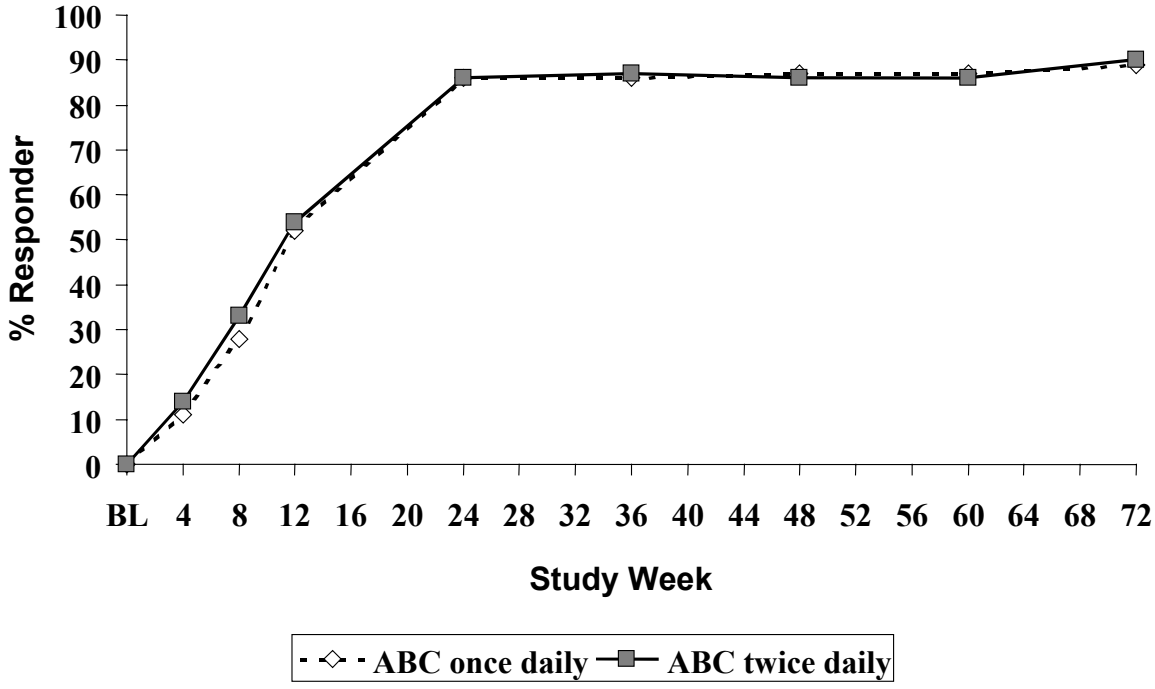


Source Data: Figure 13.3 of CNA30021 CSR.
Note: q.d. = once daily
Responders at each visit are subjects who had achieved and maintained plasma HIV-1 RNA <50 copies/mL without treatment discontinuation by that visit.

In the ITT-Exposed Population, 66% of subjects in the ABC once daily group, compared to 68% of subjects in the ABC twice daily group, achieved a virologic response of plasma HIV-1 RNA <50 copies/mL by Week 48. Sixty-nine percent of subjects received randomized study drug (ABC) for more than 48 weeks. The stratified two-sided 95% CI (-8%, 5%) demonstrates the non-inferiority of the ABC once daily treatment group as compared to the twice daily treatment group. A total of 67% (112/167) and 69% (116/169) of subjects with high viral load (>100,000 copies/mL) achieved a virological response at Week 48 in the ABC once daily and ABC twice daily groups, respectively (ITT-Exposed Population). The two-sided 95% CI (-11.6%, 8.4%) in this subgroup supports the non-inferiority of the ABC once daily treatment group as compared to the ABC twice daily treatment group. The reduced number of subjects in the high plasma HIV-1 RNA strata sub-group accounts for the wider CI.

Figure 3 highlights the consistency of response in the As-Treated Population for plasma HIV-1 RNA <50 copies/mL through Week 72.

Figure 3 Proportion of Subjects with Plasma HIV-1 RNA <50 copies/mL by Study Week (As-Treated Population - CNA30021)



	BL	W2	W4	W8	W12	W24	W36	W48	W60	W72
ABC OAD	384	341	326	317	314	300	288	266	136	45
ABC BID	386	340	339	333	326	311	294	265	144	36

Source Data: Figure 13.5 of CNA30021 CSR.

The median increase in CD4+ cell counts was comparable in each of the study groups (+188 cells/mm^3 and +200 cells/mm^3 in the once daily and twice daily groups, respectively).

The efficacy results of CNA30021 are further discussed in the Clinical Summary of Efficacy in Module 2 (m2, Section 2.7.3).

4.2.1. Populations

The median baseline plasma HIV-1 RNA and CD4+ cell counts in the populations studied in CNA30021 are typical of those initiating treatment for HIV in a clinical setting. The study had baseline stratifications to ensure that subjects with both high and low baseline plasma HIV-1 RNA were balanced between treatment groups. A total of 44% subjects had plasma HIV-1 RNA in excess of 100,000 copies/mL and 31% had CD4+ cell counts <200 cells/mm^3.

Typical of an HIV study population, the majority of subjects enrolled in CNA30021 were male but females were adequately represented (approximately 20%).

4.3. Viral Genotyping and Phenotyping

4.3.1. Introduction

ABC and 3TC are among the most effective NRTIs for lowering plasma HIV-1 RNA levels with nadir viral RNA reductions of –1.6 and –1.2 $\log_{10}$ copies/mL, respectively in monotherapy clinical studies [Eron, 1995; Saag, 1998]. Incomplete suppression of HIV-1 replication by 3TC containing regimens often rapidly selects for the M184V mutation, which decreases the plasma HIV-1 RNA reduction for 3TC to approximately –0.5 $\log_{10}$ copies/mL and decreases phenotypic susceptibility of the virus from 25 to 1000-fold relative to wild-type [Kuritzkes, 1996]. ABC can select for the M184V mutation when viral suppression is incomplete [Harrigan, 2000]. Although the effect of the M184V (in isolation) on viral suppression by ABC is minimal and the decrease in phenotypic susceptibility is only 2-3 fold, it is clear that the M184V mutation contributes to ABC resistance [Tisdale, 1997; Harrigan, 2000].

The other major mutations associated with ABC therapy are K65R, L74V and Y115F. The K65R mutation confers decreased susceptibility to ABC, 3TC, ddC, didanosine (ddI, Videx†), stavudine (d4T, Zerit†), and TDF and increased susceptibility for ZDV [Ait-Khaled, 2002]. The L74V mutation reduces susceptibility to ddI and ABC. Less is known about the Y115F mutation, but the effect on NRTI susceptibilities is small. The clinical effects of these mutations on the efficacy of most NRTIs are unknown. A detailed discussion of the genotyping and phenotyping results from study CNA30021 are provided in the Clinical Summary of Efficacy in Module 2 [m2, Section 2.7.3].

4.3.2. Pivotal study CNA30021

Use of ABC once daily compared with twice daily in combination with 3TC and EFV once daily in treatment-naïve HIV-1 infected adults

The incidence of virologic failure was low and similar across treatment groups (ABC once daily: 38/384, 10%; ABC twice daily: 32/386, 8%). Baseline genotypes and phenotypes were attempted for all subjects with virologic failure; however, due to genotype assay requirements (plasma HIV-1 RNA >500 copies/mL) only samples from 31 of the 70 subjects were evaluable on-therapy (ABC once daily n = 16; ABC twice daily n = 15).

Table 4 summarizes baseline and treatment emergent mutation data.

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† Videx is a Trade Mark of of the Bristol-Myers Squibb Company. Registered in US Patent and Trademark Office.

† Zerit is a Trade Mark of Bristol-Myers Squibb Company. Registered in US Patent and Trademark Office.

Table 4 Baseline and Treatment-emergent Mutations in Paired Samples from Subjects with Virologic Failure in Study CNA30021

Mutations	ABC OAD (n=16)	ABC BID (n=15)
Baseline		
-EFV[1]	4	1
- 3TC[2]	1	0
-TAMs[3]	5	3
-Total affected subjects	5/16	2/15
- No treatment emergent mutations (Wild type or as at baseline)	3	5
-Treatment emergent		
EFV[1]	12	14
M184V or M184I	10	5
L74V	5	3
K65R[4]	1	0
Y115F	1	1
TAMs[3]	1	1
-Total affected subjects	13/16	10/15

Source Data: GSK Report Number SM2003/00014/00, Table 8.18, Table 8.31, and Listing 6.
This table supercedes Table 22 of the CNA30021 virology report.
1. L100I, K103N, V106M, V108I, Y181C/I, Y188L, G190S/A, P225H
2. M184V/I
3. M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, K219Q/E
4. Observed in a subject with NNRTI resistance mutations at baseline.

When controlled for the presence of high level (>10-fold) reduction of phenotypic susceptibility to any study drug at baseline (ABC once daily n = 4; ABC twice daily n = 1), there was no significant difference in the number of treatment emergent mutations between the two treatment groups. There was a low overall incidence of virologic failure in both the once daily and twice daily treatment groups. This together with the low plasma HIV-1 RNA at time of virologic failure resulted in a small sample size in the virology analysis. Due to the small number of evaluable subjects and lack of apparent treatment differences, no firm conclusions can be drawn regarding differences between the two treatment groups. Selection of NRTI-associated resistance during therapy with ABC once daily is characterized mainly by the M184V mutation, selection of which might be influenced by the additional presence of 3TC.

Drug susceptibility to ZDV, d4T and TDF was retained in all 29 subjects with phenotypic data and most subjects retained clinically significant activity to ABC (ABC once daily: 13/16, ABC twice daily: 11/13).

4.4. Efficacy Conclusion

ABC and 3TC have been shown to be non-inferior when administered once daily compared to twice daily as part of combination therapy. High proportions of subjects have achieved undetectable levels of plasma HIV-1 RNA using this backbone with a variety of drugs from all three ART classes (Studies CNA30024, APV30001, APV30002, and ESS40001). Efficacy was demonstrated in subjects with both low and high baseline plasma HIV-1 RNA as well as a diverse demographic population.

In CNA30021, the pattern of NRTI mutations observed in the small proportion of ART-naïve subjects who experienced virologic failure during therapy with ABC + 3TC containing regimens was predominantly M184V only; K65R, L74V and/or Y115F mutations are uncommon. This suggests that subjects who were previously ART-naïve and fail to respond to ABC + 3TC containing regimens are likely to respond to all other agents in the NRTI class. First line ART with an ABC/3TC once daily combination regimen may therefore allow for effective treatment options in subsequent ART regimens.

5. OVERVIEW OF SAFETY

5.1. Introduction

The safety of both ABC and 3TC has been established in adults and children in multiple controlled clinical trials and corroborated by 4.5 years of post-marketing experience for ABC and 7 years of post-marketing experience for 3TC. More than 36,700 subjects have been exposed to ABC in clinical trials and approximately 434,000 patient-years of post-marketing experience with ABC containing products have been generated during the past 4.5 years up to the end of June 2003. Approximately 2,640,000 patient-years of post-marketing experience with 3TC containing products licensed to treat HIV infection have been generated during the past 7 years.

No additional pre-clinical toxicology studies were conducted to support this submission since existing studies provide data relevant to the expected plasma drug levels associated with the once daily dosing of ABC/3TC FDC.

The most significant AE associated with ABC is a drug-related hypersensitivity reaction (HSR). The HSR to ABC is a well-characterized systemic syndrome that usually presents with multiple symptoms and involves several organ systems. Rapid resolution of symptoms typically occurs following discontinuation of ABC in patients who develop HSR.

Given the established safety profiles of twice daily ABC and once daily 3TC, the key objectives in establishing the safety of the ABC/ 3TC FDC were the following:

- demonstrate that once daily ABC (600mg) had a similar safety profile to twice daily ABC (300mg) taken at the same daily dose;

- demonstrate that the incidence and/or presentation of the ABC HSR was not altered by dosing ABC once daily instead of twice daily.

Safety was assessed by monitoring clinical AEs (including pre-defined graded toxicities) and changes in laboratory parameters (hematology and clinical chemistry). Toxicity was measured according to the United States Division of AIDS standardized grading system. Any AEs not covered by these scales were graded by the investigator as mild (Grade 1), moderate (Grade 2) or severe (Grade 3 and 4). A standard definition for SAEs was used. In addition, ABC HSR was always classified as an SAE.

In this submission, pivotal study CNA30021 provides a minimum of 48-week data on the safety of ABC 600mg once daily compared to 300mg twice daily with 3TC 300mg once daily in combination with EFV in adults with HIV-1 infection. The CNA30021 CSR was generated when the last subject reached Week 48.

A detailed discussion of the safety data provided in this application is provided in the Clinical Summary of Safety in Module 2 (m2, Section 2.7.4).

5.2. Adverse Events

ABC had a similar safety profile when administered in a single daily dose as compared to a twice daily dose in subjects who participated in the pivotal study. AEs observed in CNA30021 were consistent with those described in the currently approved labeling for the ARTs administered. No new safety concerns were identified with ABC once daily dosing.

5.2.1. Pivotal Study CNA30021

Use of ABC once daily compared with twice daily in combination with 3TC and EFV once daily in treatment-naïve HIV-1 infected adults

The pivotal study CNA30021 was designed to assess the safety of ABC when administering the drug once daily instead of twice daily (at the same total daily dose). Subjects were randomized to receive ABC 600mg once-daily or 300mg twice daily, as a component of HAART including 3TC 300mg once daily and EFV 600mg once daily

The incidence of AEs (all grades) was similar in both the once daily and twice daily ABC groups and this trend continued for Grade 3/4 or severe AEs (ABC once daily, 26%, ABC twice daily, 22%). Body systems with the highest incidence of events considered by investigators to be drug-related were psychiatric disorders (ABC once daily, 35%; ABC twice daily, 36%) and nervous system disorders (ABC once daily, 32%; ABC twice daily, 28%). These AEs are well described with EFV, which was used in both treatment groups, and are therefore more likely to be due to EFV rather than the NRTI backbone. The incidences of drug-related AEs were generally comparable between treatment groups. The type and frequency of AEs leading to premature discontinuation were also similar: 16% (60/384) in the ABC once daily group and 15% (59/386) in the ABC twice daily group.

The number of Grade 3 or 4 clinical chemistry abnormalities were equally distributed across the treatment groups and no unexpected abnormalities were seen. Similar results were obtained in the analysis of the hematology results with no differences being seen between the two treatment groups.

In this double-blind study there is no evidence suggesting any change in the safety profile of ABC when administered once daily rather than twice daily. None of the safety parameters indicate any increased risk with once daily ABC and it is re-assuring to note that the profile of HSR is unchanged. Overall, the ABC + 3TC backbone had an acceptable safety profile. HSR is described in Section 5.2.3 of this overview.

5.2.2. Deaths, Serious Adverse Events, and Withdrawals Due to an Adverse Event

In study CNA30021, the incidences of serious adverse events (SAEs) were generally comparable between treatment groups with 17% (67/384) of subjects in the ABC once daily group experiencing a SAE compared to 16% (62/386) of subjects in the ABC twice daily group. There were five subject fatalities (2 in the once daily group and 3 in the twice daily group) and one fatality in the offspring of a study subject; none of these deaths were considered by the investigator to be attributable to study drug.

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

5.2.3. Abacavir Hypersensitivity Reaction

The HSR to ABC is a recognizable syndrome characterized by the presence of multiple symptoms that indicate involvement of several organs or systems. GSK guidance for the management of ABC HSR is conservative and states that ABC should be discontinued as soon as the diagnosis is suspected or if the diagnosis cannot be ruled out. Typically, rapid resolution of HSR symptoms occurs following discontinuation of ABC in patients who develop HSR. Rechallenge reactions can be more severe and, in some cases, life threatening or fatal. GSK is committed to educating healthcare professionals (HCPs) and patients about the risk of developing a HSR to the ABC/3TC FDC tablet and about avoiding rechallenge with ABC-containing products. For details of these programs, refer to Module 1 (m1, Section 1.8.1).

GSK recognizes that there may be concerns about the potential increased risk of developing a HSR with ABC 600mg administered once daily. There is no theoretical basis for this concern since there is not a simple dose-response relationship for idiosyncratic drug reactions. In addition, neither the widely accepted theory for explaining these reactions (the hapten hypothesis, in which a reactive metabolite binds to a protein forming an adduct that triggers the reaction) nor an alternative theory (the danger hypothesis in which the reaction is triggered by a sensitized immune system) depend on drug exposure or drug levels [Naisbitt, 2003].

In the pivotal double-blind trial CNA30021, the incidence of suspected ABC HSR was similar in subjects taking ABC once daily (9%) versus subjects taking ABC twice daily (7%). The incidence of suspected ABC HSR in this study was similar to other double-blind studies in which HSR reports were solicited using the ABC HSR CRF module. This incidence is likely to reflect the proactive method of data collection, investigator education and the lowered threshold for reporting HSR, e.g., in the presence of overlapping drug toxicities, rather than a true incidence rate [Hernandez, 2003]. The clinical presentation of suspected ABC HSR was similar in subjects taking ABC once a day versus subjects taking ABC twice a day and was consistent with current ABC product labeling.

An ad hoc analysis was performed and compared the signs and symptoms of ABC HSR reported in CNA30021 with a previous analysis performed on 9 clinical trials with 206 ABC HSR cases (refer to Section 2.1.5. of the Clinical Summary of Safety [Module 2, m2]). Specific individual symptoms reported with ABC HSR and relative frequencies of signs and symptoms were comparable between the two analyses and between the ABC once daily and ABC twice daily treatment groups. The median time to onset of ABC HSR was 9 days for both treatment groups in CNA30021 and in the previous analysis of nine clinical trials. The majority (90%) of ABC HSRs occurred within the first 6 weeks of ABC exposure. This is consistent with previous experience and the current ABC product labeling.

As described below, data from three clinical trials utilizing ABC 600mg doses do not suggest a difference in ABC HSR rates with dose escalation.

- CNAA2001 was a Phase I/II multiple dose escalation trial designed to evaluate the safety and PK of ABC as monotherapy and in combination with ZDV. Doses of ABC studied were 200mg, 400mg and 600mg administered every 8 hours (cohorts I [N=19], II [N=20], and IV [N=20]) and 300 mg administered every 12 hours (Cohort III [N=20]). The total daily dose of ZDV was 600 mg in each cohort. There were 3/59 (5%) ABC HSRs experienced when ABC was administered as 200mg, 400mg or 600mg every 8 hours (1 in each of Cohorts I, II and IV). No ABC HSRs were observed when ABC 300mg was administered every 12 hours in Cohort III. Although the sample size was small, there was not an increased rate of ABC HSR when the total daily dose of ABC was increased up to 1800mg.
- CNAB2002 was designed to further define the appropriate dose of ABC and to determine the durability of antiretroviral effects. ABC doses given were 100mg, 300mg or 600mg twice daily. The rates of ABC HSR were 5% (1/19) in the ABC 300mg twice daily group and 6% (1/18) in the 600mg twice daily group.
- CNAB3001 was a Phase III study designed to evaluate the effect of ABC compared to placebo in combination with stable background therapy in subjects with AIDS associated dementia. Two percent of subjects (2/83) receiving ABC 600mg twice daily developed an ABC HSR.

In a risk factor analysis of 34 protocols comprising more than 8,000 ABC exposed subjects, baseline weight was not a predictor of HSR, suggesting that drug exposure or drug levels are not determinants of HSR risk [Cutrell, 2003].

GSK recognizes the concerns about the HSR to ABC in the marketed products, **ZIAGEN** and **TRIZIVIR,** and the potential added concern that multiple marketed products containing ABC could lead to confusion and, thus, accidental rechallenge in patients who have experienced an ABC HSR. GSK has implemented significant educational activities to alert HCPs and patients to the risk of HSR and about avoiding rechallenge with either **ZIAGEN** or **TRIZIVIR**. GSK is committed to educating HCPs and patients about the risk of developing an ABC HSR to the ABC/3TC FDC tablet and about avoiding rechallenge with the ABC containing products. Cases involving HSR to ABC and rechallenge reactions are closely monitored by the company. To date, no HSR rechallenge cases have been received in which the decision to restart **ZIAGEN** or **TRIZIVIR** was due to a lack of knowledge of the ABC component of the formulation.

GSK is committed to continue to educate HCPs about ABC HSR and to monitor the risk of HSR, rechallenge HSR, and HSR-related death following the introduction of the ABC/3TC FDC tablet to the market.

5.2.4. Laboratory Data

In the pivotal efficacy study CNA30021, the incidence of treatment-emergent abnormalities (i.e., changes from baseline values and Grade 3/4 abnormalities) for clinical chemistry and hematology parameters was generally low and comparable among treatment groups. The abnormalities seen were not clinically significant and were similar to abnormalities reported in the product label for each of the administered treatments.

A detailed discussion of laboratory data changes from baseline and Grade 3 and 4 treatment-emergent abnormalities is provided in Sections 3.2 and 3.3 of the Clinical Summary of Safety, Module 2 (m2, Section 2.7.4);

5.3. Safety Conclusions

The safety of both ABC and 3TC has been established in adults and children in multiple controlled clinical trials and corroborated by 4.5 years of post-marketing experience for ABC containing products and 7 years of post-marketing experience for 3TC containing products (indicated to treat HIV-1 infection), comprising more than 434,000 and 2.64 million patient-years of exposure, respectively. The data included in this submission are consistent with the data previously submitted in support of **ZIAGEN** and **EPIVIR** products.

Both ABC and 3TC had acceptable safety profiles in ART-naïve, HIV-1 infected subjects who participated in pivotal study CNA30021. The type, incidence, and severity of AEs reported in CNA30021 were consistent with those reported in previous clinical trials, and no new safety issues were identified.

The incidence and presentation of suspected ABC HSRs were similar in subjects taking ABC once daily versus subjects taking ABC twice daily.

No changes to the recommended diagnosis and management of suspected ABC HSR are indicated based on the available data from clinical trials and post-marketing surveillance.

6. OTHER INFORMATION

6.1. Ongoing GSK-Sponsored Studies

For complete disclosure, the following ongoing studies sponsored by GSK evaluating the ABC/3TC FDC tablet as a component of ART are listed:

CAL30001: This randomized, open-label, parallel group, multicenter study was designed to evaluate treatment with the ABC/3TC FDC (600mg/300mg) once-daily versus ABC (300mg) twice daily and 3TC (300mg) once daily in combination with TDF once daily and a new PI or NNRTI for 48 weeks in ART-experienced HIV-1 infected subjects with virologic failure.

ESS30008: This randomized, multicenter study was designed to compare the safety and efficacy of the ABC/3TC FDC tablet administered once daily with the two tablets, ABC + 3TC, administered twice daily as a component of a triple ART. The regimen includes a PI or NNRTI over 48 weeks of therapy in ART-experienced HIV-1 infected subjects with virologic suppression and currently receiving ABC and 3TC as single entities.

ESS30009: This randomized, open-label, multicenter study was designed to evaluate the safety and durability of EFV + ABC/3TC once daily versus TDF + ABC/3TC once daily over 48 weeks in approximately 306 ART-naive subjects. Subjects with plasma HIV-1 RNA ≥5000 copies/mL were eligible for inclusion. The primary endpoint is the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48.

As previously noted, shortly after initiation of this study, reports of poor virologic response in subjects receiving TDF + ABC/3TC were observed. An expedited unplanned analysis was conducted to assess virologic non-response, defined as either (a) failure to achieve a 2 $\log_{10}$ copies/mL decrease from baseline by treatment Week 8 or (b) a 1 $\log_{10}$ copies/mL increase above nadir on any subsequent treatment visit. A total of 49% and 48% of patients reaching 8 and 12 weeks of therapy met these criteria in the TDF + ABC/3TC group versus 5% at both 8 and 12 weeks in the EFV + ABC/3TC group. Preliminary genotypes of viral isolates from 14 patients with virologic non-response taking the TDF + ABC/3TC regimen have shown all 14 isolates had the M184V mutation in HIV reverse transcriptase. In addition, 8 of the 14 (57%) isolates also had the K65R mutation. Based on these results, the TDF + ABC/3TC treatment group of this study was recently terminated.

Data from study ESS30009 relates to the use of TDF + ABC/3TC as triple ART and the nature of any interaction between the components of this regimen is being investigated. This study indicates that ABC/3TC should not be used with TDF as part of triple anti-retroviral therapy. Other studies included in this and previous submissions indicate that ABC/3TC can be effectively used as a nucleoside backbone with other third agents from the NRTI (ZDV, d4T), PI, and NNRTI class of drugs.

Studies CAL30001 and ESS30008 are currently ongoing and no data are available.

In addition to GSK sponsored studies, other GSK supported studies employ ABC once daily and/or 3TC once daily regimens. Safety data for these studies are described in the Clinical Summary of Safety in Module 2 (m2, Section 2.7.4).

7. BENEFITS AND RISKS CONCLUSIONS

7.1. Therapeutic Justification

Both ABC and 3TC are proven, highly effective NRTIs. The combination of ABC and 3TC has a low potential for drug-drug interactions and has demonstrated broad compatibility with existing treatment options. In addition, ABC and 3TC have acceptable safety profiles with minimal potential for overlapping toxicities with other ARTs.

The ABC/3TC FDC tablet provides a NRTI backbone as one tablet administered once a day with no food or fluid restrictions/requirements. These characteristics are expected to increase patient satisfaction and/or adherence and may help maximize long term treatment efficacy.

7.2. Efficacy

Bioequivalence of the FDC tablet of ABC 600mg/3TC 300mg to the single entity products, **ZIAGEN** (2 X 300mg tablets) and **EPIVIR** (2 X 150mg tablets), has been demonstrated by CAL10001. Also, as demonstrated in CNA10905, the geometric mean intracellular terminal half-life of CBV-TP (20.64 hours) supports the use of ABC 600mg once daily for the treatment of HIV infected patients.

In CNA30021, substantial and sustained virologic suppression and immunological responses were observed through 48 weeks when ABC was administered once daily or twice daily in combination with 3TC and EFV once daily. CNA30021 demonstrated that ABC once daily was non-inferior to ABC twice daily.

The ABC/3TC FDC tablet provides a favorable resistance profile that may preserve future treatment options.

7.3. Safety

The type, incidence, and severity of AEs reported in the pivotal study were consistent with that reported in previous clinical trials. Most AEs were Grade 1 to 2, mild to moderate in severity and not treatment limiting.

The incidence and presentation of reported HSRs in the ABC once daily group was comparable to that in the ABC twice daily group suggesting no increase in risk with once daily dosing.

7.4. Risk: Benefit Ratio

The data in this application support a favorable benefit/risk ratio with the ABC/3TC FDC tablet administered once daily. The ABC/3TC FDC tablet is the first combination nucleoside backbone administered as one tablet once daily, without food or fluid restrictions/requirements and may simplify treatment regimens. This may be useful in poorly compliant populations and in patients receiving other multiple therapies. Other advantages of the ABC/3TC FDC include the low potential for significant drug-drug interactions or mitochondrial toxicity combined with a favorable resistance profile that may preserve future treatment options.

The benefits of treatment with the ABC/3TC FDC tablet need to be balanced with the risk of toxicity. No additional safety concerns are expected for the ABC/3TC FDC tablet over those seen for **ZIAGEN** and **EPIVIR** used in combination. Additive toxicities between ABC and 3TC have not generally been problematic in clinical studies. In view of the intended clinical use, GSK believes the introduction of the combination tablet will pose no new or previously uncharacterized risk. The main safety issue with the proposed tablet is the HSR to ABC. Clinical trials utilizing ABC 600mg administered once daily or in multiple ABC 600mg doses have demonstrated a similar incidence and clinical presentation of ABC HSR relative to the licensed 300mg twice daily dose.

Reported cases involving the HSR to ABC and rechallenge reactions are closely monitored by GSK. In particular, the reasons behind the decision to restart **ZIAGEN** or **TRIZIVIR** are assessed in detail and described in the biannual HSR reports submitted to the Food and Drug Administration (FDA). To date, no HSR rechallenge cases have been received in which the decision to re-start **ZIAGEN** or **TRIZIVIR** was due to a lack of knowledge of the ABC content of the formulation. GSK is committed to educating HCPs and patients about the risk of developing an ABC HSR to the ABC/3TC FDC tablet and about avoiding rechallenge with ABC containing products.

ABC and 3TC are already used in combination HIV therapy and can provide clinical benefit in a variety of treatment strategies as mentioned above. The ABC/3TC FDC is a more convenient form of this combination and does not present additional safety concerns. The overall assessment of the risk/benefit ratio for the ABC/3TC FDC is favorable and the once a day tablet represents an important new treatment option for HIV-1 infected patients.

7.5. Overall Conclusion:

The ABC/3TC FDC tablet is a potent antiretroviral combination with an acceptable safety profile that can be given without dietary or fluid restrictions. This combination tablet has a low potential for drug-drug interactions and can be combined with many other therapies for HIV and opportunistic infections. The ABC/3TC FDC tablet, the first combination nucleoside backbone offered as one tablet administered once daily, has the potential to be used as part of once daily, highly active antiretroviral treatment regimens. The ABC/3TC FDC tablet provides an important option in the management of HIV disease.

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