The GlaxoSmithKline group of companies

Title:

Module 2.7.2 Summary of Clinical Pharmacology-ABC/3TC (abacavir sulfate + lamivudine) Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection

Author(s):	Signature:	Date:
, Ph.D. Clinical Pharmacology & Discovery Medicine		09/9/03

Approver(s):	Signature:	Date:
, Ph.D. Clinical Pharmacology & Discovery Medicine		Sept 22. 03

Module 2.7.2

Summary of Clinical Pharmacology

TABLE OF CONTENTS

PAGE

ABBREVIATIONS

3TC	lamivudine **(EPIVIR†)**
ABC	abacavir (**ZIAGEN†)**
AE	Adverse Event
$AUC_{0\text{-}t,ss}$	Area under the drug concentration-time curve from 0 to time t at steady state
AUC_{∞}	Area under the plasma concentration versus time curve from time 0 and extrapolated to infinity
BID	Twice daily
CBV-TP	Carbovir triphosphate
CSF	Cerebrospinal Fluid
CI	Confidence interval
CL/F	Apparent Clearance
C_{max}	Maximum drug concentration
$C_{max,ss}$	Maximum drug concentration at steady state
CSF	Cerebrospinal Fluid
$C_{t,ss}$	Concentration at t hours post dose at steady state
ddC	Zalcitabine (Hivid†)
DP	Diphosphate
EFV	Efavirenz (Sustiva†)
EU	European Union
FDC	Fixed Dose Combination
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
h	Hour(s)
HIV	Human Immunodeficiency Virus
HSR	Hypersensitivity reaction
kg	Kilogram
L	Liter
λ_z	Elimination rate constant
mg	Milligram(s)
mL	Milliliter(s)
MP	Monophosphate
µg	Microgram(s)
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PBL	Peripheral Blood Lymphocyte
PD	Pharmacodynamics
PK	Pharmacokinetics
R	Accumulation ratio
$t_{½}$	Elimination half-life

ABBREVIATIONS CONTINUED

t_{max}	Time to Maximum Concentration
$t_{max,ss}$	Time to Maximum Concentration
TP	Triphosphate
US	United States
ZDV	Zidovudine (**RETROVIR**†)

1. BACKGROUND AND OVERVIEW OF CLINICAL PHARMACOLOGY

The clinical pharmacology of abacavir (ABC) and lamivudine (3TC) have been extensively studied in both healthy volunteers and HIV-infected patients. This section of the submission presents an overview of the clinical pharmacology of ABC and 3TC (Section 1.1) and the rationale for once-daily dosing of ABC (Section 1.2). Lastly, summary results are presented from a recent clinical pharmacology study, CNA10905, to characterize plasma ABC and intracellular carbovir triphosphate (CBV-TP, the active moiety of ABC) pharmacokinetics in support of once daily dosing of ABC as a component of the fixed dose combination (FDC) tablet of ABC/3TC (600mg/300mg) for the treatment of HIV infection (Section 2).

1.1. Overview of Clinical Pharmacology of Abacavir and Lamivudine

1.1.1. Abacavir

The clinical pharmacology of abacavir (ABC) has been extensively characterized in the submissions for **ZIAGEN**[†] and is briefly summarized in this section for reference.

ABC is moderately lipophilic, has good water solubility, and shows rapid dissolution in neutral and acidic media. ABC has excellent absolute oral bioavailability (~83%). The apparent volume of distribution after intravenous administration is approximately 0.8 L/kg, suggesting that ABC distributes into extravascular space. Whole body autoradiography studies in mice have shown that after oral administration ABC-related ^{14}C-material is widely distributed throughout the body. Measurable concentrations of ABC were found in brain and/or cerebrospinal fluid (CSF) in mice, monkeys, and humans. An *in vitro* study using primary bovine brain endothelial cells (an established blood-brain-barrier model) has shown that ABC permeates the brain endothelial cells by a passive diffusion mechanism and its permeability is greater than that of zidovudine (ZDV). Binding to plasma proteins is moderate, approximately 50%. ABC is extensively metabolized by the liver, with less than 2% of the dose excreted as unchanged drug in the urine. It is primarily metabolized via two pathways, UDP-glucuronyl transferase and alcohol dehydrogenase, resulting in the inactive glucuronide metabolite (361W94, ~ 36% of dose) and the inactive 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 recovered. The terminal elimination half-life of ABC is approximately 1.5 hours and is consistent over a dose range of 300 to 1200mg single-dose administrations. Following multiple oral doses of abacavir 300mg twice a day there is no significant accumulation of ABC.

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

Linear pharmacokinetics are observed for ABC from single doses of 600 to 1200mg and at steady-state following repeat doses of 300mg twice a day (600mg daily) up to 600mg three times daily (1800mg daily). After oral administration of a single 600mg dose of ABC in 20 patients, Cmax was 4.26 ± 1.19 µg/mL (mean ± standard deviation [SD]) and AUC was 11.95 ± 2.51 µg*h/mL. At 300mg twice daily, the steady-state peak plasma concentration ($C_{max,ss}$) of ABC is approximately 3.0 ± 0.9 µg/mL and overall exposure ($AUC_{0-12,ss}$) is approximately 6.02 µg*h/mL.

The extent of ABC absorption (AUC_{∞}) is not affected by food intake (standard high fat breakfast: total calories 967 kcal, 24% carbohydrate, 14% protein and 62% fat). However, administration of ABC with a high-fat meal did reduce the rate of absorption, as evidenced by a decrease in C_{max} of about 25-35% and delayed t_{max} of about 0.5 to 1.5 hrs. The effect of food on ABC bioavailability is consistent with observations for other nucleoside analogs and is primarily due to a delay in gastric emptying after food intake. The differences in t_{max} and C_{max} are not considered clinically relevant since AUC of ABC has shown to be better correlated with its efficacy and no pharmacokinetic parameter has shown significant correlation with toxicity [Weller, 2000].

ABC is not significantly metabolized by cytochrome P450 enzymes, nor is it involved in the induction or inhibition of these enzymes. Therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways. Due to different elimination pathways, no clinically significant drug interaction has been observed between ABC and 3TC. Although ABC and ZDV share a common metabolic glucuronidation pathway, no clinically relevant changes in the pharmacokinetics of either ABC or ZDV have been observed with their concurrent administration.

Coadministration of ethanol and ABC 600mg was studied in 24 HIV-infected males and resulted in an increase in mean ABC AUC_{∞} by 41%; however, this change is not considered clinically relevant. ABC had no effect on the pharmacokinetic properties of ethanol. This interaction has not been studied in females. HIV-infected patients 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. This alteration may require an increased methadone dose in a small number of patients.

Effects of gender and ethnic origin were evaluated by a population pharmacokinetic analysis of ABC concentrations from four Phase II/III studies and the results indicated that potential differences in ABC pharmacokinetics based on race or gender are due to differences in lean body weight [GSK Document Number RM2000/00510/00]. However, the magnitude of this effect is insufficient to require any dosage adjustments based on body size in adults.

Age related changes in ABC pharmacokinetics are observed in pediatric subjects, especially in children younger than 2 years old, resulting in lower exposures for a given mg/kg dose compared to adults. Pediatric subjects require higher mg/kg doses than adults, presumably due to increased metabolic rate. The current recommended oral dose of **ZIAGEN** for pediatric patients is 8 mg/kg twice daily (up to a maximum of 300mg twice daily) in combination with other antiretroviral agents.

There are limited data for ABC in renal dysfunction. ABC pharmacokinetics have been studied in six end stage renal disease HIV-infected patients and no changes were observed for ABC pharmacokinetics. ABC pharmacokinetics have been evaluated in patients with mild hepatic impairment (Child-Pugh score of 5-6) and the data showed statistically significant 89%, 26% and 58% increases, respectively, in ABC AUC_{∞}, C_{max} and $t_{½}$ after a single oral 600mg dose in these patients compared to patients with normal hepatic function. These changes suggested that ABC daily dose should be reduced in patients with mild hepatic impairment due to altered ABC pharmacokinetics.

1.1.2. Lamivudine

The clinical pharmacology of lamivudine (3TC) has been extensively characterized in submissions for **EPIVIR**† and is briefly summarized in this section for reference.

3TC is a high solubility and high permeable drug with rapid dissolution. Consistent with these properties, all formulations have shown rapid oral absorption with peak concentrations generally achieved in 0.8 to 1.5 hours. The bioavailability of oral 3TC in adults is typically between 80 and 85%. Autoradiography studies in rat, and animal and human pharmacokinetic studies have demonstrated that 3TC is widely distributed throughout the body. The apparent volume of distribution after intravenous administration is approximately 1.3 L/kg. Binding of 3TC to human plasma proteins is low (<36% to serum albumin *in vitro*). The mean systemic clearance of 3TC is approximately 0.32 L/h/kg, with predominantly renal clearance (>70% of unchanged drug) via glomerular filtration and active tubular secretion. Hepatic metabolism of 3TC to the sulphoxide metabolite accounts for only 5-10% of an administered dose. The observed elimination half-life of 3TC is 5 to 7 hours.

Dose linearity was demonstrated for both AUC_{∞} and C_{max} for doses ranging from 0.5 to 20mg/kg/day in adults after single- and multiple-dose oral administration. Values for λ_z, $t_{1/2}$ and CL/F were independent of dose over this dose range. 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 (AUC24,ss) was 8.87 ± 1.83 µghr/mL. The average accumulation ratio (R) of 1.48 is observed between first dose and steady-state. This is consistent and predictable from the terminal half-life observed in single dose studies (ranging 5-7 hours) and a 12-hour dosing interval.

3TC has no known clinically relevant food interactions. 3TC administration is not recommended for coadministration with zalcitabine (ddC, Hivid†) due to mutual inhibition of intracellular phosphorylation. 3TC elimination is inhibited by trimethoprim

---

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

† Hivid is a Trade Mark of Roche Laboratories.
Registered in US Patent and Trademark Office.

which results in an increase in 3TC AUC of ~ 40%; however, no dosing adjustment is required. 3TC can be given with all currently marketed antiretrovirals, except for ddC.

There are no significant gender or racial differences in 3TC pharmacokinetics. Age-related pharmacokientic changes of 3TC have been observed in pediatric patients. The recommended oral dose of 3TC for HIV-infected pediatric patients is 4 mg/kg twice daily (up to a maximum of 150mg twice a day), administered in combination with other antiretroviral agents.

The pharmacokinetic properties of 3TC have been determined in a small group of HIV-infected adults with impaired renal function. Exposure (AUC_∞), C_{max}, and half-life of 3TC increased with diminishing renal function. Based on these observations, it is recommended that the dosage of 3TC should be modified in patients with renal impairment. The pharmacokinetic properties of 3TC have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for 3TC is required for patients with impaired hepatic function.

1.2. Rationale for Once Daily Dosing for Abacavir

The ABC/3TC FDC tablet was developed specifically for once daily administration. The current recommended daily dose for 3TC is 300mg administered as once or twice a day. The once daily dosing regimen for 3TC 300mg has already been approved in major regulatory markets including the US and EU. The currently recommended dose of ABC for the treatment of HIV infection is a daily dose of 600mg administered as 300mg twice a day. This section presents the rationale for the once daily dosing regimen for ABC 600mg.

ABC is anabolized in infected and uninfected human T-lymphoblastoid CD4+ CEM cells (CEM-T4) and in uninfected peripheral blood lymphocytes (PBLs) to carbovir-triphosphate (CBV-TP), the only triphosphate observed intracellularly after incubation with ABC. The intracellular metabolic profile of ABC has been characterized in CD4+ CEM cells after a 48-hour or shorter period of incubation with 10 μM of ABC. The parent and metabolites of ABC measured intracellularly included ABC, CBV, amino-CBV, ABC-MP, CBV-MP, amino-monophosphate (non-quantifiable due to interferences), CBV-DP, and CBV-TP. Intracellular CBV-TP is considered the active intracellular moiety of ABC for inhibition of HIV reverse transcriptase and it has an intracellular half-life of 3.3 hrs in CEM cells [Faletto, 1997]. Additionally, CBV-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 [Faletto, 1997]. This is unlike previously studied nucleoside reverse transcriptase inhibitors (NRTIs) which have at least one saturable formation step to the active triphosphate.

Recent preclinical and clinical data have suggested that once daily administration of ABC is also possible in the treatment of HIV-1 infection. In the hollow fiber model, an *ex vivo* pharmacodynamic system, comparable viral suppression was obtained with ABC 600mg administered once daily compared with ABC 300mg administered every 12 hours

[Bilello, 1997; Drusano, 2002]. Other external academic studies, conducted with HIV-infected patients, investigated the intracellular concentrations of CBV-TP and found that the elimination half life of the intracellular triphosphate was longer than 12 hours and that inhibitory concentrations were maintained over 24 hours with either 300mg twice daily or 600mg once daily dosing [Kewn, 2000; Harris, 2002]. These findings supported the conduct of clinical investigations of once daily ABC administration for the treatment of HIV-1 infection and development of a combination tablet containing ABC 600mg and 3TC 300mg. The administration of ABC as 600mg once daily should not change its drug-drug interaction profile.

1.3. Clinical Pharmacology Studies

Study CNA10905 was conducted by GSK to further investigate the intracellular pharmacokinetics of CBV-TP, using a validated assay, consistent with Good Laboratory Practice, to support the once daily dosing of ABC. This was an open-label, single arm, pilot study in twenty HIV infected patients who were on a stable ABC-containing regimen. The intracellular pharmacokinetics of CBV-TP at steady state were determined following administration of an ABC 300mg twice-daily containing regimen (**ZIAGEN** or **TRIZIVIR**[†]). Study CNA10905 is described in Section 2. A tabulated summary of the study design is provided in Table 2. A tabulated summary of pharmacokinetic parameters for plasma ABC and intracellular CBV-TP observed in Study CNA10905 is included in Table 4.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. Study CNA10905

Study Title: **An Open Label, Single Arm, Pharmacokinetic Study of Abacavir and its Intracellular Anabolite Carbovir Triphosphate Following Chronic Administration of an Abacavir 300mg BID containing Regimen (ZIAGEN or TRIZIVIR) in HIV Infected Patients**.

2.1.1. Objectives

The primary objective of Study CNA10905 was to describe the intracellular pharmacokinetics of CBV-TP at steady-state following administration of an ABC 300mg twice-daily containing regimen (**ZIAGEN** or **TRIZIVIR**) in HIV infected patients.

The secondary objective was to describe the pharmacokinetics of ABC in plasma, and its relationship to intracellular CBV-TP, at steady state following the administration of an ABC 300mg twice-daily containing regimen (**ZIAGEN** or **TRIZIVIR**) in HIV infected patients.

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

2.1.2. Study Design and Data Analysis

This was an open-label, single arm, pharmacokinetic (PK), pilot study in HIV infected patients who were currently on a stable ABC-containing regimen for at least 6 weeks. Screening evaluations were performed in an outpatient setting of a maximum of 30 days and a minimum of 7 days prior to PK sampling (Day 1). Patients meeting entry criteria were entered into the study the evening (Day -1) prior to a 24-hour PK sampling during which the second dose was withheld. Subjects remained in the clinic until the morning of Day 2, after the PK sampling was complete.

Safety was assessed by adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, urinalysis, and pregnancy testing), vital signs assessments, concurrent medications, and monitoring of possible ABC hypersensitivity reaction (HSR).

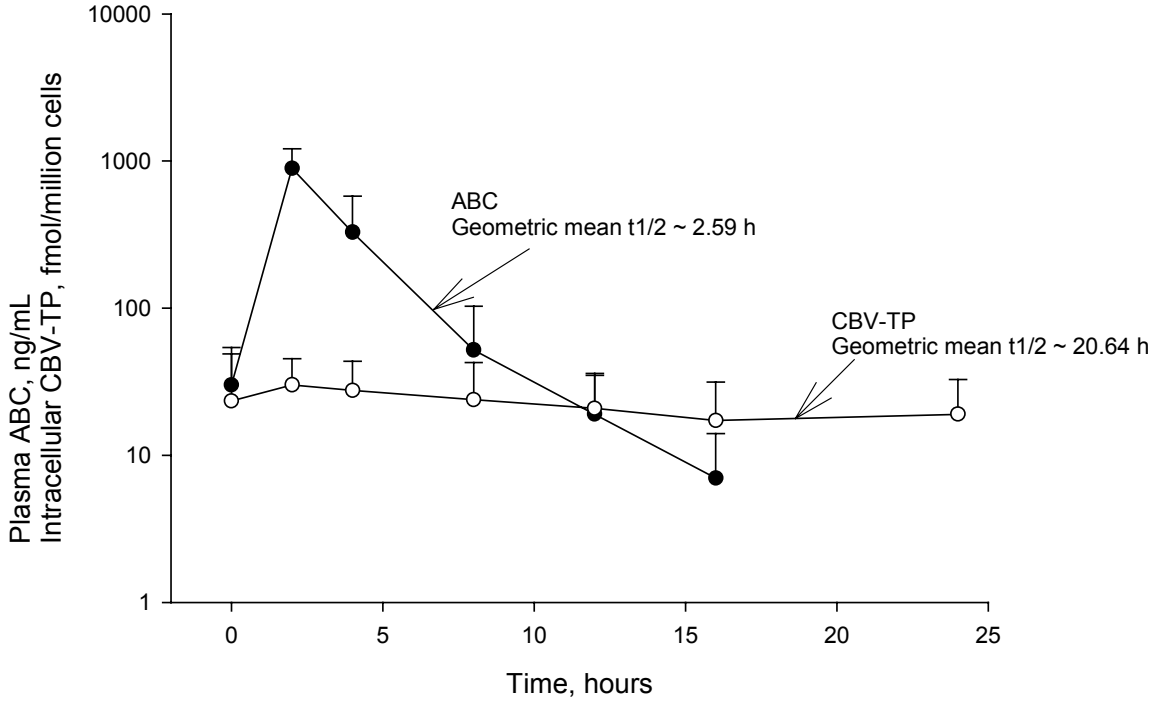
For the PK evaluations, two sets of blood for plasma ABC and intracellular CBV-TP were collected over a 24-hour period as follows: Pre-dose (within 30 minutes prior to dose) and 2, 4, 8, 12, 16 and 24-hours after dosing. Steady state plasma ABC and intracellular CBV-TP PK parameters, including $AUC_{0\text{-}24,ss,}$ $C_{max,ss}$, $C_{24,ss}$, $t_{max,ss,}$ λ_z and $t_{½}$, were estimated by standard noncompartmental methods using WinNonlin Professional version 3.1 (Pharsight Corporation, Mountain View, CA, USA). Descriptive statistics were calculated for each of the PK parameters; Geometric Mean and 95% confidence interval (CI) for these PK parameters were provided. There were no treatment comparisons in this study.

2.1.3. Results

Twenty subjects were enrolled and completed the study and were included in the Safety and PK Populations. Nine subjects were on a current stable regimen of **ZIAGEN** (ABC 300mg twice daily) and 11 subjects were on a current stable regimen of **TRIZIVIR** (ABC 300mg + 3TC 150mg + ZDV 300mg twice daily).

Figure 1 shows the mean concentration-time profiles of plasma ABC and intracellular CBV-TP at steady state observed in Study CNA10905.

Figure 1 Study CNA10905: Mean (SD) Concentration-time Profiles of Plasma ABC and Intracellular CBV-TP up to 24 Hours Post Dose at Steady State Following a ABC 300mg Twice Daily Containing Regimen



Note: Blood samples were collected up to 24 hours post dose with the second dose on the same day skipped.
Source data: m5, GSK Document Number RM2002/00405/00, Table 12.3 and Table 12.5.

At steady state, following 300mg ABC twice daily, the observed plasma ABC concentrations reached its peak value of 0.88 µg/mL (geometric mean, 95% CI: 0.75-1.03 µg/mL) at approximately 2.00 hours after dose administration. The area under the concentration-time curve for plasma ABC from time 0 to 24 hours post dose ($AUC_{0\text{-}24,ss}$) had a geometric mean of 2.56 µg*h/mL (95% CI: 2.13-3.06 µg*h/mL). The terminal half-life of plasma ABC was described by a geometric mean of 2.59 hours (95% CI: 2.04-3.29 hours).

The intracellular CBV-TP concentration time profile demonstrated a flat terminal curve from approximately 8-12 hours through 24 hours. Intracellular CBV-TP PK parameter estimates are summarized below in Table 1. The CBV-TP has a prolonged intracellular

terminal half-life of a geometric mean of 20.64 hours (95% CI: 16.39-25.99 hours). The maximum intracellular concentration of CBV-TP, $C_{max,ss}$, has a geometric mean of 29.66 fmol/10^6cells (95% CI: 22.07-39.86 fmol/10^6cells). The intracellular CBV-TP concentration at 12 hours post dose (the end of the dosing interval for a twice daily dosing regimen), $C_{12,ss}$, had a median of 18.1 fmol/10^6cells with a range of 4.7-51.6 fmol/10^6cells. Large inter-subject variability was observed in the intracellular pharmacokinetics of CBV-TP.

Table 1 Selected Intracellular Carbovir Triphosphate PK Parameter Estimates

Parameter	Geometric Mean (N=20)	95 % CI
$AUC_{0-24,ss}$, (fmol*h/10^6cells)	252.78	190.05 – 336.21
$C_{max,ss}$, (fmol/10^6cells)	29.66	22.07 – 39.86
$t_{½}$, (h)	20.64	16.39 – 25.99
	Median	**Min – Max**
$C_{12,ss}$, (fmol/10^6cells)	18.1	4.7 – 51.6
$C_{24,ss}$, (fmol/10^6cells)	16.35	3.1 – 61.1
$t_{max,ss}$, (h)	2.00	0.00 – 12.00

Source data: m5, GSK Document Number RM2002/00405/00, Table 12.5 and Table 12.9.

The intracellular pharmacokinetics of CBV-TP were similar whether subjects were receiving ABC as **ZIAGEN** or as **TRIZIVIR**. The intracellular half-life of CBV-TP ranged from 6.28 to 35.42 hours for subjects receiving ABC as **ZIAGEN** (n=9) and from 9.56 to 48.1 hours for subjects receiving ABC as **TRIZIVIR** (n=11). The AUCs for ABC in plasma and for intracellular CBV-TP were similar between the two treatment regimens.

HIV-1 infected subjects on a **ZIAGEN** (300mg ABC) containing antiviral regimen or **TRIZIVIR** (300mg ABC + 150mg 3TC + 300mg ZDV) containing regimen for ≥6weeks continued to tolerate their stable regimens well. Therefore, as expected, there were no drug-related AEs, serious adverse events, abacavir hypersensitivity reactions, or deaths reported during this study. No subjects withdrew from this study due to an AE. A total of six AEs were reported by four subjects. No AE was reported more than once. No clinically significant laboratory abnormalities were reported. No vital signs, ECG or physical examination results were recorded as AEs.

Overall there were no significant changes in CD4+ cell counts or HIV-1 RNA copies/mL from withholding one dose of ABC in subjects who were tolerating it for at least 6 weeks. As would be expected, CD4+ cell counts remained consistent from screening to 24h

post-dosing during the study. Fifteen subjects maintained HIV-1 RNA ≤400 copies/mL, two subjects had decreased HIV-1 RNA copies/mL, two subjects had a small increase in HIV-1 RNA levels from screening to 24h post-dosing and one subject's screening viral load was unevaluable.

2.1.4. Discussion and Conclusions

Discussion

The plasma pharmacokinetics of ABC observed in Study CNA10905 were similar to those observed in previous studies in HIV infected patients. The prolonged intracellular terminal half-life of CBV-TP observed in this study confirmed the results by Kewn [2000] and Harris [2002]. The observed CBV-TP concentrations in Study CNA10905 were generally lower than those observed by Kewn [2000] and Harris [2002]. The differences in observed concentrations may be due to several factors including the small number of subjects in those two external studies, differences in cell processing and differences in assay methodology. The two studies by Kewn [2000] and Harris [2002] used a non-GLP validated competitive template primer binding versus the more specific GLP validated assay used in Study CNA10905.

Intracellular CBV-TP concentrations observed in Study CNA10905 were on average approximately 2 fold greater than the reported Ki value for incorporation of endogenous dGTP into DNA by HIV-1 reverse transcriptase of 21 nmol/L [Daluge, 1997] throughout the 24-hour interval, with concentrations of approximately 20 fmol/10^6 cells (or approximately 40 nmol/L).

The short plasma half-life of ABC along with long terminal half-life of intracellular CBV-TP suggests that there is a pooling of one of the precursors of CBV-TP (e.g., ABC-MP, CBV-MP or CBV-DP) within the cell. Although Study CNA10905 was conducted in patients receiving ABC 300mg twice daily, similar intracellular kinetics for CBV-TP are expected after ABC 600mg once daily due to the pooling mechanism of one of the precursors of CBV-TP inside the cell. Kewn [2000] demonstrated that intracellular CBV-TP at steady state ranged from a mean of about 50 fmol/10^6 cells at trough concentration to approximately 150 fmol/10^6 cells at peak concentration, using a non-GLP validated enzymatic assay, following a ABC 300mg twice daily dosing regimen. Using the same enzymatic assay, Harris [2002] showed that intracellular CBV-TP levels at steady state following a ABC 600mg once daily dosing regimen were maintained above 100 fmol/10^6 cells on average over the entire 24-hour dosing interval. These external studies suggested that the average trough intracellular concentration of CBV-TP following an ABC 600mg once daily dosing regimen is expected to be greater than or equal to that following an ABC 300mg twice daily dosing regimen. The pivotal clinical efficacy study CNA30021, presented in Module 2, 2.7.3, Summary of Clinical Efficacy of this submission, established the non-inferiority of the ABC 600mg once daily + 3TC 300mg once daily + EFV (Sustiva†) 600mg once daily treatment group as

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

compared to the ABC 300mg twice daily + 3TC 300mg once daily + EFV 600mg once daily treatment group. Therefore the results from Study CNA10905, demonstrating a prolonged intracellular CBV-TP half-life, are supportive of the clinical efficacy results.

Conclusions

- The observed intracellular CBV-TP concentrations and its pharmacokinetics with the prolonged terminal half-life (geometric mean of 20.64 hours with 95% confidence interval of 16.39-25.99 hours) support the clinical investigations for the use of ABC 600mg once daily for the treatment of HIV infected patients.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

Not applicable due to a single clinical pharmacology study submitted (see Section 2, Summary of Results of Individual Studies).

Conclusions

- A prolonged intracellular CBV-TP half-life of greater than 20 hours was observed from 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 are necessary.

4. REFERENCES

Bilello JA, Bilello PA, et al. 1592U89, a novel carbocyclic nucleoside inhibitor of reverse transcriptase, limits HIV replication in an in vitro hollow fiber pharmacodynamic model. 37th Intersci Conf Antimicrob Agents Chemother (ICAAC), Toronto, Canada, 1997;225.

Daluge SM, Good SS, Faletto MB, et al. 1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity. Antimicrob Agents Chemother 1997;41:1082-1093.

Drusano GL, Bilello PA, Symonds WT, et al. Pharmacodynamics of abacavir in an in vitro hollow-fiber model system. Antimicrob Agents Chemother 2002;46(2):464-470.

Faletto MB, Miller WH, Garvey EP, St. Clair MH, Daluge SM, and Good SS. Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. Antimicrob Agents Chemother 1997;41:1099-1107.

GSK Document RM2000/00510/00. Population-Based Pharmacokinetic Analysis of Abacavir Concentrations from Four Phase II/III Clinical Trials. 06 June 2003.

GSK Document Number RM2002/00405/00. Clinical Study Report of An Open Lable, Single Arm, Pharmacokinetic Study of Abacavir and its Intracellular Anabolite Carbovir Triphosphate Following Chronic Administration of an Abacavir 300mg BID Containing Regimen (**ZIAGEN** or **TRIZIVIR**) in HIV Infected Patients. 8 April 2003.

Harris M, Back D, Kewn S, et al. Intracellular carbovir triphosphate levels in patients taking abacavir once a day. AIDS 2002;16(8);1197-1198.

Kewn, S, Maher B, Hoggard PG, et al. The pharmacokinetics of abacavir phosphorylation in peripheral blood mononuclear cells from HIV positive subjects. Presented at the 5th International Congress on Drug Therapy in HIV Infection, Glasgow, United Kingdom, October 22-26, 2000. Poster 276A (abstract published in AIDS. Volume 14, Suppl. 4 Oct 2000).

Weller S, Radomski KM, Lou Y, Stein DS. Population pharmacokinetics and pharmacodynamic modeling of abacavir (1592U89) from a dose-ranging, double-blind, randomized monotherapy trial with human immunodeficiency virus-infected subjects. Antimicrob Agents Chemother. 2000; 44(8):2052-60.

5. SECTION 1 APPENDIX

Table 2 Tabular Listing of all Clinical Pharmacology Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status;	Location of Study Report
CNA10905	PK/PD	Intracellular triphosphate PK	Open label	HIV-infected patients	20 (12 Male/ 8 Female) Age 40.0 y (29-55y)	Abacavir 300 mg BID containing regimen (**ZIAGEN** or **TRIZIVIR**)	Complete	m5, GSK Document Number RM2002/00405/00

Table 3 Glossary for Summary Results of Clinical Pharmacology PK Studies

Protocol No.	The Study identifier.
Study Design:	Degree of blinding : open, single blind, or double blind Treatment assignment: random or nonrandom Treatment sequence: crossover, parallel or dose escalation
Number of subjects (M/F):	Number of subjects/patients who received study medication; (number of males M/ females F)
Age Mean Range:	Provides the mean and range of ages in years
Treatment Details (Drug/Dose/Form/Route/Frequency):	Study treatments are identified Dose (mg) of each treatment as specified in the protocol (e.g. BID=twice daily)
$AUC_{0-24,ss}$	Area under the concentration versus time curve from time zero to 24 hours post dose at steady state
$C_{max,ss}$	Maximum observed concentration at steady state
$t_{½}$	Apparent terminal elimination half-life
$t_{max,ss}$	Time to reach the maximum observed concentration at steady state
$C_{12,ss}$	Concentration at 12 hours post dose (end of dosing interval) at steady state
$C_{24,ss}$	Concentration at 24 hours post dose at steady state

2.7.2 Summary of Clinical Pharmacology

Table 4 Summary Results for All Clinical Pharmacology Pharmacokinetic Studies

Protocol No.	Study Objective(s)	Study Design	No. of Subjects; Gender M/F Mean Age (Range); Subject Inclusion Criteria	Treatment Details (Drug/Dose/ Form/Route/ Frequency/Duration)	Analyte	Pharmacokinetic Parameters						Study Report Location
						$AUC_{0-24,ss}$[1]	$C_{max,ss}$[1]	$t_{1/2}$[1] (h)	$t_{max,ss}$[2] (h)	$C_{12,ss}$[2]	$C_{24,ss}$[2]	
CNA10905	Intracellular triphosphate PK	Open label	20 (12 M/8 F) 40y(29-55y) HIV-infected patients	**ZIAGEN** 300mg BID/tablet/oral or **TRIZIVIR** ABC 300mg, 3TC 150mg and ZDV 300mg BID/tablet/oral	ABC CBV-TP	2.56 (2.13-3.06) 252.87 (190.05-336.21)	0.88 (0.75-1.03) 29.66 (22.07-39.86)	2.59 (2.04-3.29) 20.64 (16.39-25.99)	2.00 (2.00-3.92) 2.00 (0-12.00)	 18.1 (4.7-51.6)	 14.94 (10.59-21.06)	M5, GSK Document Number RM2002/00405/00

Note:
Units: AUC in μg*h/mL for ABC and fmol*h/10^6cell for CBV-TP; C in μg/mL for ABC and fmol/10^6 cell for CBV-TP.
1. Geometric Mean (95% CI)
2. Median (range)