CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-652

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21652
Submission Dates: 10/07/2003
Brand Name: Epzicom
Generic Name: Lamivudine/ Abacavir sulfate
Formulation: 300/600 mg tablet
Applicant: GlaxoSmithKline
Reviewer: Jenny H. Zheng, Ph.D.
Team Leader: Kellie Reynolds, Pharm.D.
OCPB Division: DPE III
ORM Division: DAVDP

Table of Contents

I. Executive Summary

Abacavir (ABC), a guanosine analogue, and lamivudine (3TC), a cytosine analogue, are nucleoside reverse transcriptase inhibitors (NRTIs). Both products are approved for the treatment of HIV infection in combination of other antiretroviral drugs. Once daily dosing of lamivudine is approved. Abacavir is approved for twice daily dosing; the NDA for once daily dosing of abacavir was submitted (NDA 20977, SE2-012) on October 2, 2003. The approval of the ABC/3TC combination tablet is dependent on the approval of abacavir once daily dosing. The ABC/3TC combination tablet (as a component of combination therapy) is expected to improve adherence to a regimen already established in clinical practice. The pivotal bioequivalence study, CAL10001, confirmed the bioequivalence of the fixed dose combination tablet to equivalent doses of Ziagen® and Epivir®.

A. Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant is acceptable.

B. Phase IV Commitments

None.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical pharmacology of abacavir (ABC) and lamivudine (3TC) have been extensively studied in both healthy volunteers and HIV-infected patients. The current submission only includes one pivotal bioequivalence study, which compares the bioavailability of ABC/3TC combination tablet relative to equivalent doses of the marketed Ziagen® and Epivir®. The study also evaluated the effect of food on the bioavailability of ABC/3TC formulation. As shown in the following table, bioequivalence was achieved for both abacavir and lamivudine following coadministration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to sequential administration of the currently marketed products Epivir® and Ziagen®.

PK Parameter	Geometric LS Mean[a]		Ratio of Geometric LS Means A/B	90% CI
	Treatment A N=25	Treatment B N=25		
Abacavir				
AUC_{last} (ug*h/mL)	14.12	14.12	1.000	0.955-1.048
AUC_{∞} (ug*h/mL)	14.15	14.15	1.000	0.954-1.048
C_{max} (ug/mL)	4.68	4.94	0.946	0.855-1.048
Lamivudine				
AUC_{last} (ug*h/mL)	12.36	13.00	0.951	0.910-0.995
AUC_{∞} (ug*h/mL)	12.60	13.23	0.952	0.912-0.994
C_{max} (ug/mL)	2.64	2.84	0.930	0.865-0.999

Treatment A = Fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted;
Treatment B = **ZIAGEN** (2 x 300 mg) + **EPIVIR** (2 x 150 mg) Fasted
Treatment C = Fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed
a based on log-transformed data.

Following administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) in the fed state, a lack of effect of food on the rate and extent of bioavailability of lamivudine was demonstrated. The extent of bioavailability of abacavir was unaffected in the fed state, compared to the fasted state, but the Cmax was reduced. These results are similar to those from previous studies of the effect of food on ABC and 3TC tablets given separately. Both ABC and 3TC can be given with or without food, and thus ABC/3TC can be given with or without food.

PK Parameter	Geometric LS Mean[a]		Ratio of Geometric LS Means C/A	90% CI
	Treatment A N=25	Treatment C N=25		
Abacavir				
AUC_{last} (ug*h/mL)	14.12	12.74	0.902	0.861-0.945
AUC_{∞} (ug*h/mL)	14.15	12.79	0.903	0.862-0.947
C_{max} (ug/mL)	4.68	3.54	0.757	0.684-0.838
Lamivudine				
AUC_{last} (ug*h/mL)	12.36	11.89	0.962	0.920-1.006
AUC_{∞} (ug*h/mL)	12.60	12.13	0.963	0.922-1.005
C_{max} (ug/mL)	2.64	2.27	0.860	0.800-0.924

Treatment A = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted
Treatment B = **ZIAGEN** (2 x 300 mg) + **EPIVIR** (2 x 150 mg) Fasted
Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed

a based on log-transformed data.

The sponsor also provided the dissolution method and the dissolution specification for ABC/3TC formulation, as shown below:

Apparatus: Paddle, USP dissolution apparatus 2
Rotation: 75 rpm
Temperature: 37 °C
Medium: 900 mL of ——
Specification: Q = —— at 30 min.

The proposed dissolution method and dissolution specification are acceptable.

We requested a Division of Scientific Investigations inspection of the clinical and analytical sites for the bioequivalence study. The inspection results indicate that the bioequivalence study conduct and analytical procedures were acceptable.

II. Question Based Review

A. General Attributes

a) *What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?*

Abacavir sulfate and lamivudine drug substances used in this product are the same, and are sourced from the same sites, as those for the approved Ziagen® (abacavir sulfate) Tablets, Epivir® (lamivudine) Tablets. Please see Clinical Pharmacology and Chemistry reviews for NDA 20-977, NDA 20-564 and all supplement and amendments.

The product is a tablet for oral administration containing 600 mg of abacavir (as abacavir sulfate) and 300 mg of lamivudine. The composition of abacavir-lamivudine tablets is given below.

Component	Quantity mg/tablet	Function	Reference to Standard
Tablet Core			
Abacavir Sulfate	—	Active	GlaxoSmithKline
Lamivudine	300	Active	GlaxoSmithKline
Microcrystalline Cellulose		—	NF
Sodium Starch Glycolate			NF
Magnesium Stearate		—	NF
Total Core Tablet Weight	1375		
Film Coat			
Opadry® Orange YS-1-13065-A	41[2]	Film Coat	Supplier

Note:
1. Equivalent to 600 mg Abacavir per tablet based on a —
2. The tablet target film coat weight is — based on a theoretical weight gain of
3.

b) What is the proposed mechanism of drug action and therapeutic indication?

Abacavir (ABC), a guanosine analogue, and lamivudine (3TC), a cytosine analogue, are nucleoside reverse transcriptase inhibitors (NRTIs). The principle mechanism of action for the active moieties of ABC and 3TC is the inhibition of the HIV-1 reverse transcriptase (RT) enzyme via chain termination after incorporation of the nucleoside analogues into viral deoxyribonucleic acid (DNA). Both products are approved for the treatment of HIV infection in combination of other antiretroviral drugs.

c) What is the proposed dosage and route of administration?

The proposed dose of lamivudine/abacavir 300 mg/600 mg for adults and adolescents is one tablet daily given orally, in combination with other antiretroviral agents.

d) What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

No pivotal clinical study was conducted with lamivudine/abacavir combination tablets.

B. General Clinical Pharmacology

No new information was submitted. See clinical Pharmacology reviews for NDA 20-977, NDA 20-564.

C. Intrinsic Factors

No new information was submitted. See Clinical Pharmacology reviews for NDA 20-977 and NDA 20-564.

D. Extrinsic Factors

No new information was submitted. See Clinical Pharmacology reviews for NDA 20-977 and NDA 20-564.

E. General Biopharmaceutics

a) *What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?*

A pivotal BE study (CAL 10001) was conducted to compare the bioavailability of ABC/3TC combination tablet relative to equivalent doses of the marketed Ziagen® and Epivir®. As shown in the following table, bioequivalence was achieved for both abacavir and lamivudine following coadministration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to sequential administration of the currently marketed products Epivir® and Ziagen®.

PK Parameter	Geometric LS Mean[a]		Ratio of Geometric LS Means A/B	90% CI
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Treatment C = Fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed
a based on log-transformed data.

b) *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

The pivotal BE study (CAL 10001) also evaluated food effect on the pharmacokinetics of abacavir and lamivudine. As shown in the following table, following administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) in the fed state, a lack of effect of food on the rate and extent of bioavailability of lamivudine was demonstrated. The extent of bioavailability of abacavir was unaffected in the fed state, compared to the fasted state, but the Cmax

was reduced. These results are similar to those from previous studies of the effect of food on ABC and 3TC tablets given separately. Both ABC and 3TC can be given with or without food, and thus ABC/3TC can be given with or without food.

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Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed

a based on log-transformed data.

c) *How do the dissolution conditions and specifications assure in vivo performance and quality of the product?*

The method for the determination of dissolution of abacavir and lamivudine from Abacavir-Lamivudine Tablets is the same as the approved method for Ziagen® (abacavir sulfate) and Trizivir® (zidovudine, lamivudine, abacavir sulfate)Tablets, as shown below.

Apparatus: Paddle, USP dissolution apparatus 2
Rotation: 75 rpm
Temperature: 37 °C
Medium: 900 mL of ———
Specification: Q = — at 30 min.

The rationale for selecting this method is summarized here.

Selection of dissolution medium

The dissolution medium of — hydrochloric acid (HCl) used for abacavir/lamivudine combination tablets is the same dissolution medium as that approved for Ziagen® Tablets and for Trizivir® Tablets. The sponsor indicated the use of — HCl maximizes the differences in the UV spectra of abacavir and lamivudine allowing the use of multicomponent UV analysis. Multicomponent UV analysis was used for Trizivir® Tablets to determine the concentrations of abacavir and lamivudine in the multicomponent Sample Solution.

The in vitro dissolution characteristics of the bioequivalence batch of Abacavir-Lamivudine Tablets in several media were studied. The sponsor indicated that greater than — abacavir and lamivudine are dissolved in 30 minutes across a range of biologically relevant pHs (data not provided). These results indicated that Abacavir-Lamivudine Tablets are rapidly dissolved. These observations are consistent with previous data for Ziagen® and Trizivir®. The selected dissolution medium is acceptable.

Selection of dissolution apparatus and rotation speed

Paddle is used as a dissolution apparatus for Ziagen® and Trizivir® Tablets, and is selected for abacavir/lamivudine combination tablets. The paddle rotation speed was

Table 1 Dissolution Results for Abacavir-Lamivudine Tablets
Batch 18129-001-12 at

Tablet	% Dissolved					
	Abacavir			Lamivudine		
	15 minutes	30 minutes	45 minutes	15 minutes	30 minutes	45 minutes
1 2 3 4 5 6 7 8 9 10 11 12						
Mean	76	97	98	76	99	100
Min						
Max						
% RSD	13.3	1.4	1.4	12.7	4.5	4.2

Table 2 Dissolution Results for Abacavir-Lamivudine Tablets
Batch 18129-001-12 at 75 RPM

Tablet	% Dissolved					
	Abacavir			Lamivudine		
	15 minutes	30 minutes	45 minutes	15 minutes	30 minutes	45 minutes
1 2 3 4 5 6 7 8 9 10 11 12						
Mean	89	99	100	90	101	101
Min						
Max						
% RSD	10.4	1.1	1.5	11.3	3.2	3.2

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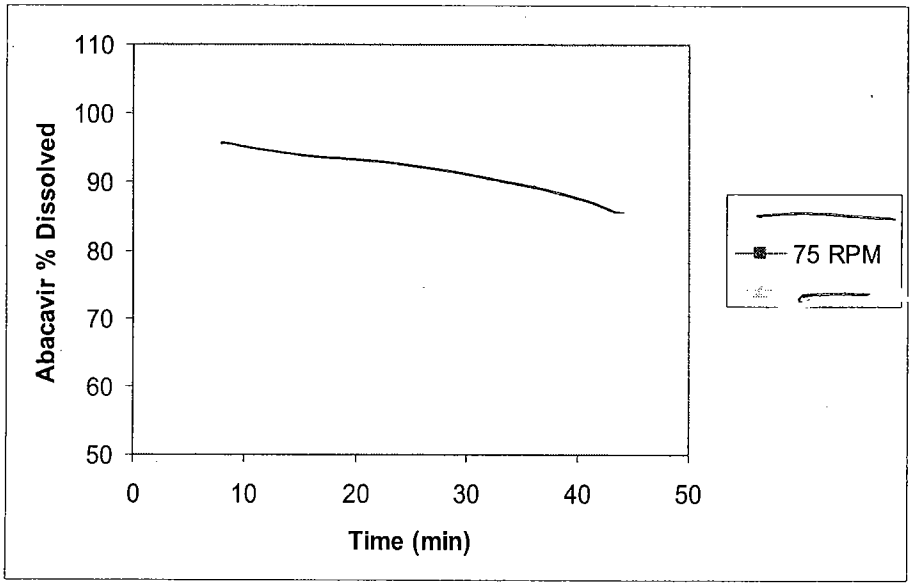
Table 3 Dissolution Results for Abacavir-Lamivudine Tablets
Batch 18129-001-12 at

Tablet	% Dissolved					
	Abacavir			Lamivudine		
	15 minutes	30 minutes	45 minutes	15 minutes	30 minutes	45 minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	97	100	100	100	103	103
Min						
Max						
% RSD	5.9	0.9	0.9	6.4	3.4	3.4

The following figures show the mean % dissolved abacavir and lamivudine at otation speeds.



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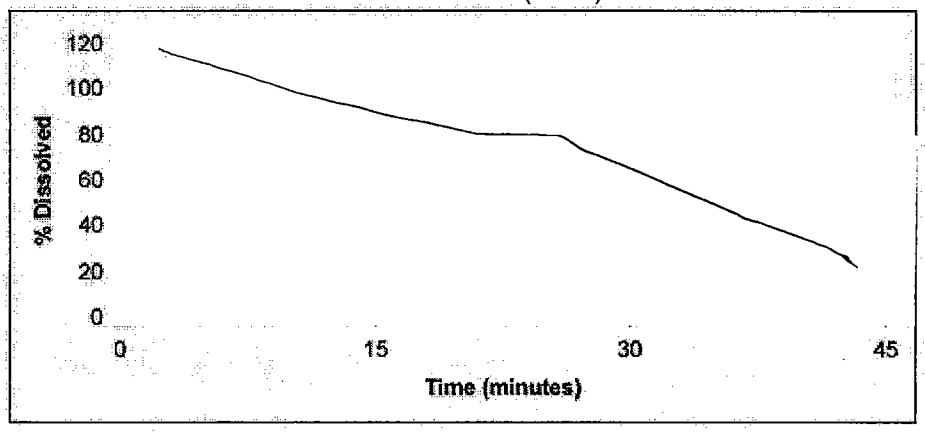
✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1 of 2

Dissolution Profile of Lamivudine in Abacavir-Lamivudine Tablets, Batch B060661 (n=12)



Dissolution Results for Abacavir-Lamivudine Tablets Batch B060661 Used in Bioequivalence Study CAL10001

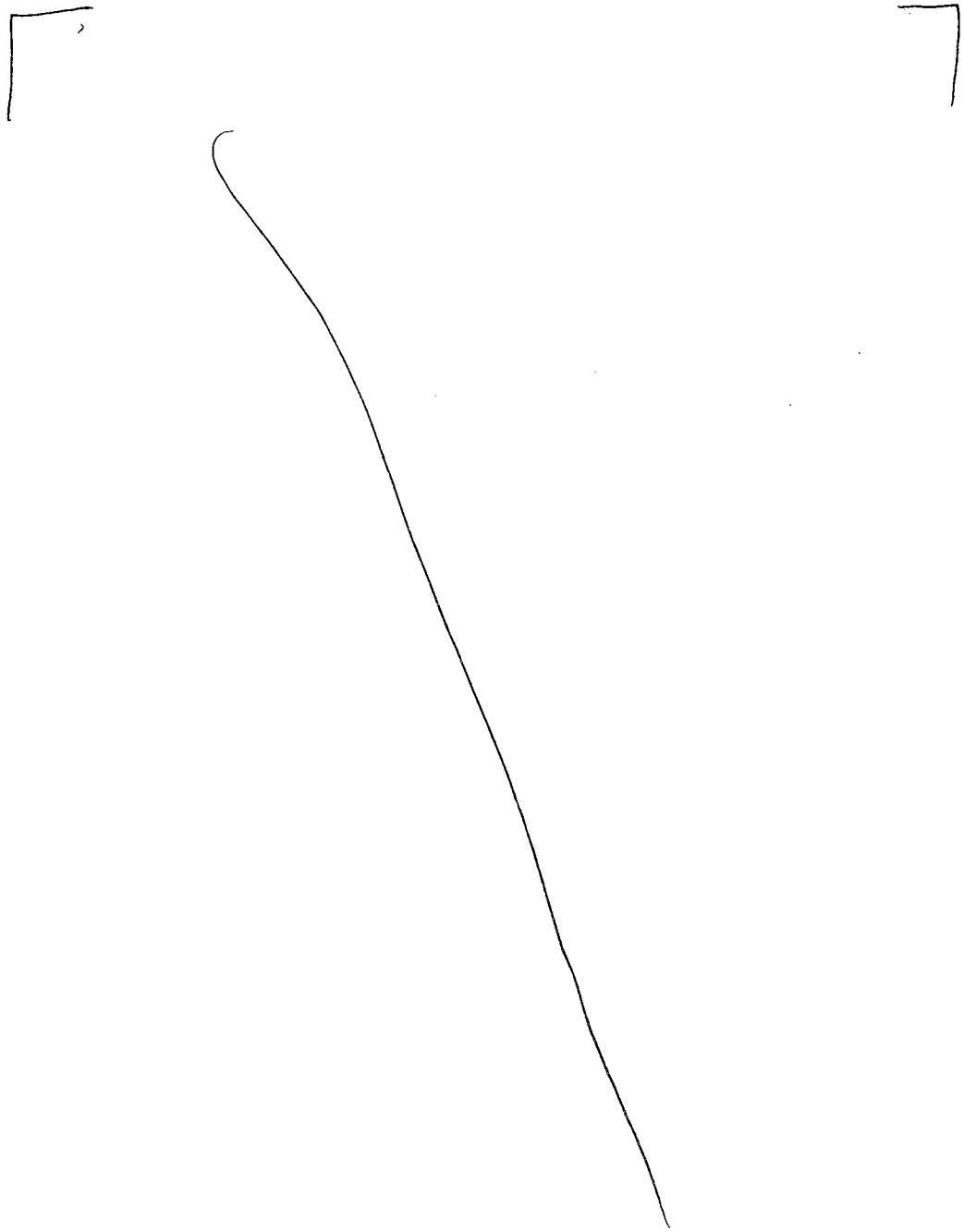
Tablet	% Dissolved					
	Abacavir			Lamivudine		
	15 minutes	30 minutes	45 minutes	15 minutes	30 minutes	45 minutes
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	70	100	101	70	102	102
Min						
Max						
% RSD	14.4	2.3	2.5	13.8	2.8	2.9

The dissolution profiles for the batch of abacavir-lamivudine tablets used in bioequivalence study CAL10001 demonstrate that the product is highly soluble and rapidly dissolving. The results from individual dissolution profiles for batches used for other clinical and stability studies (Batch B060662, B062405, and B086990, submitted on 11/21/2003) also complied with the proposed specification of Q = ⟶ abacavir and lamivudine dissolved in 30 minutes. Therefore, the dissolution specification set by the sponsor is acceptable.

F. Analytical Section

The standard curve and QC data indicated that the plasma assay methods for abacavir and lamivudine were precise and accurate as shown in the individual review for Study CAL 10001 (Page 20).

III. Labeling Recommendation



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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2of2

Jenny H. Zheng, Ph.D.
Reviewer, Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence:

Kellie S. Reynolds, Pharm. D
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

cc: HFD-530 /NDA 21652
/MO/AJames
PM/TSinha
HFD-880 /JHZheng
HFD-880 /TL/KReynolds

IV. Individual Study Report Reviews

An Evaluation of the Bioequivalence of a Combined Formulated Tablet (600mg /300mg abacavir/lamivudine) Compared to Ziagen® (abacavir) 2 X 300mg Tablets and Epivir ® (lamivudine) 2 X 150mg Tablets Administered Concurrently and the Effect of Food on Absorption of the Combined Formulation in Healthy Adult Subjects (Study CAL 10001)

Objectives:

- To evaluate the bioequivalence between a single tablet composed of 600mg abacavir and 300mg lamivudine versus the treatment of Ziagen® (abacavir) 2 x 300mg tablet and Epivir® (lamivudine) 2 x 150mg tablet administered sequentially.
- To evaluate food effect on the absorption of the new combination formulation of abacavir/lamivudine.

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

Study Design: This was a single-center, open-label, randomized, single-dose, three-way crossover study. All subjects who completed screening were allocated to receive one of the three treatments in each period, in a randomized, balanced fashion, using a random code based on two 3 X 3 Latin squares.

Treatment Sequence

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

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

Treatment B: ZIAGEN (abacavir) 2 x 300mg tablet and EPIVIR (lamivudine) 2 x 150mg tablet sequentially following an overnight fast,

Treatment C: Fixed dose combination of abacavir/lamivudine (600 mg/300 mg) five minutes following a standardized breakfast.

There was a washout period of 5 to 10 days between each dose.

Formulation: Batch numbers for investigational product are provided in the table below.

Study Drug	Dose	Batch Number
Ziagen® tablet	300mg	1ZP2321
Epivir® tablet	150mg	1ZP2545
abacavir/lamivudine tablet	600mg/300mg	B060661

Sample Analysis: Human plasma samples were assayed for abacavir and lamivudine using validated HPLC/MS/MS methods. The standard curve and QC data indicated that the plasma assay methods for abacavir and lamivudine were precise and accurate as shown in the following table.

Analyte	Linear range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)	Validation sample for stability and conditions
Abacavir		≤ 7.07			• Stable ≥ 12 hours at room temperature • Stable for at least 3 freeze thaw cycles • Plasma sample extracts were stable for at least 96 h at room temperature.
Lamivudine		≤ 6.78			

PK Analysis: Blood samples were collected at pre-dose (within 30 minutes prior to dose) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after dosing during each of the three treatment periods.

Results: The following figures show the plots of mean plasma abacavir (ABC) and lamivudine (3TC) concentration-time profiles.

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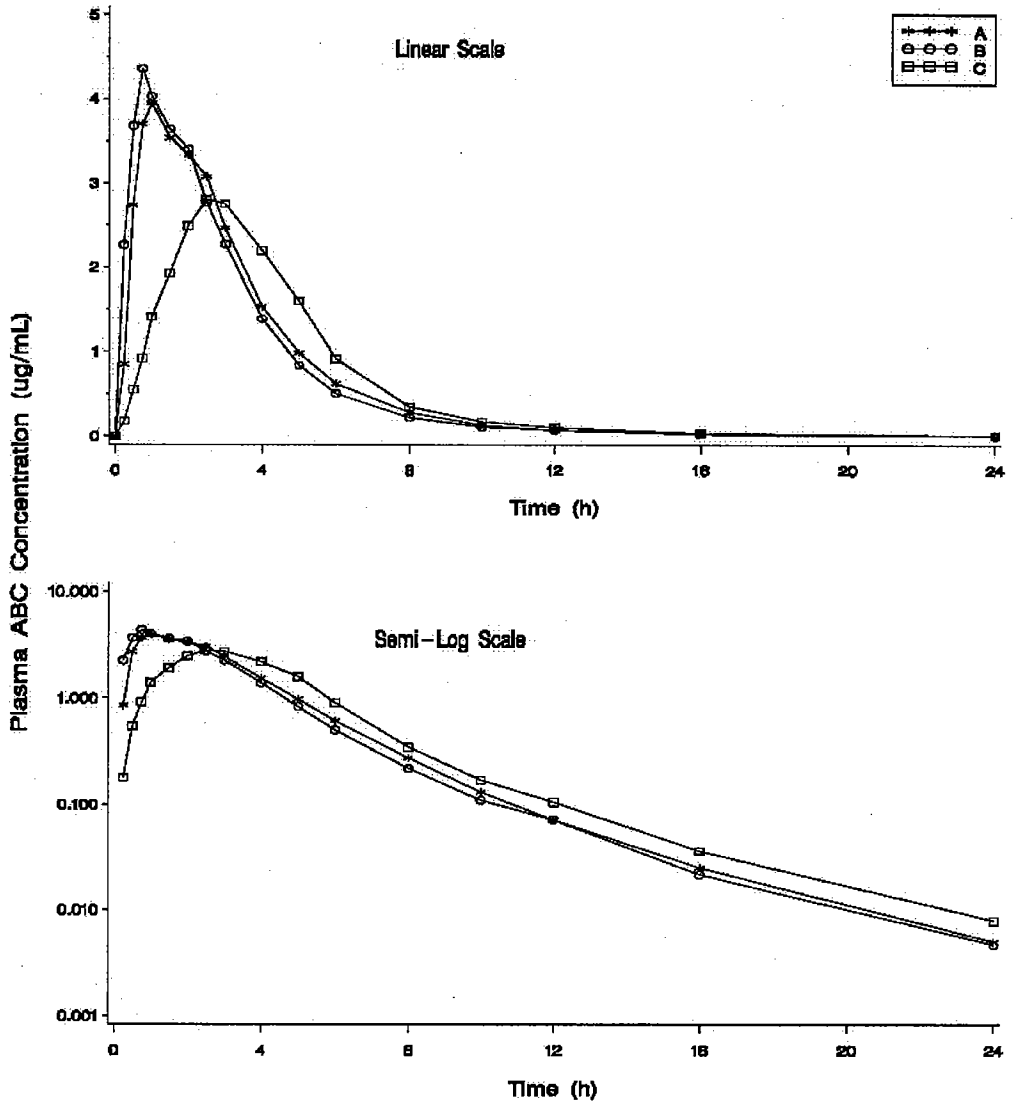
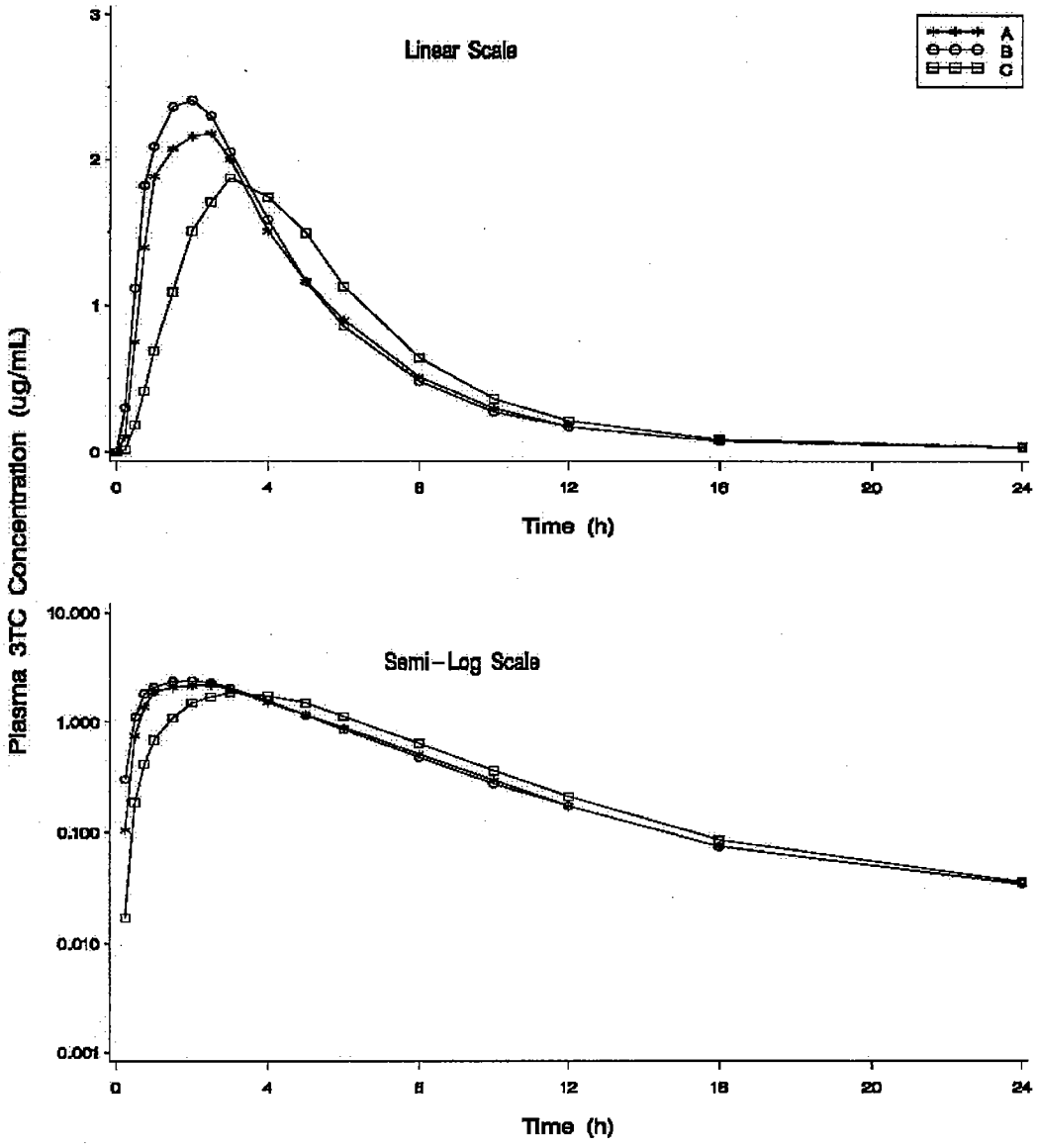


Subject 30, Period 2, Treatment C, 0.25 hr sample was excluded
Treatment A = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fasted
Treatment B = ZIAGEN (abacavir) 2X300 mg and EPIVIR (lamivudine) 2X150 mg Fasted
Treatment C = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fed

Plot of Mean Plasma 3TC Concentration–time Profiles



Subject 30, Period 2, Treatment C, 0.25 hr sample was excluded
Treatment A = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fasted
Treatment B = ZIAGEN (abacavir) 2X300 mg and EPIVIR (lamivudine) 2X150 mg Fasted
Treatment C = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fed

Derived pharmacokinetic parameters for ABC and 3TC are summarized in the following tables.

Plasma ABC Pharmacokinetic Parameter Estimates:
Geometric Mean (95% CI); Pharmacokinetic Summary Population

Plasma APV PK Parameter	Treatment A N=25	Treatment B N=25	Treatment C N=25
AUC_{last} (µg.h/mL)	14.18 (12.91-15.58)	14.15 (12.87-15.55)	12.77 (11.58-14.08)
AUC_{∞} (µg.h/mL)	14.21 (12.94-15.61)	14.18 (12.90-15.59)	12.81 (11.61-14.13)
C_{max} (µg/mL)	4.69 (4.15-5.30)	4.91 (4.46-5.41)	3.52 (3.13-3.95)
t_{max} (h)[a]	1.00 (0.50-3.00)	0.75 (0.25-3.00)	2.50 (1.00-5.00)
$t_{½}$ (h)	2.92 (2.67-3.19)	2.86 (2.59-3.17)	3.04 (2.79-3.31)

Treatment A = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted
Treatment B = **ZIAGEN** (2 x 300 mg) + **EPIVIR** (2 x 150 mg) Fasted
Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed

a t_{max} values are median (range).

Plasma 3TC Pharmacokinetic Parameter Estimates:
Geometric Mean (95% CI); Pharmacokinetic Summary Population

Plasma APV PK Parameter	Treatment A N=25	Treatment B N=25	Treatment C N=25
AUC_{last} (µg.h/mL)	12.34 (11.41-13.35)	12.95 (11.97-14.01)	11.85 (11.04-12.72)
AUC_{∞} (µg.h/mL)	12.57 (11.64-13.58)	13.18 (12.20-14.24)	12.08 (11.27-12.96)
C_{max} (µg/mL)	2.64 (2.37-2.95)	2.82 (2.61-3.05)	2.26 (2.07-2.46)
t_{max} (h)[a]	2.00 (1.00-5.00)	1.50 (0.75-4.00)	3.00 (1.00-5.00)
$t_{½}$ (h)	4.93 (4.63-5.26)	4.99 (4.74-5.25)	4.86 (4.57-5.17)

Treatment A = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted
Treatment B = **ZIAGEN** (2 x 300 mg) + **EPIVIR** (2 x 150 mg) Fasted
Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed

a t_{max} values are median (range).

For the bioequivalence portion of the study, the 90% confidence intervals for the ratio (Treatment A: Treatment B) of the geometric LS means for AUC_{last}, AUC_{∞} and C_{max} for both ABC and 3TC were completely contained within the predefined equivalence range of 0.80-1.25. Abacavir (ABC) and Lamivudine (3TC) pharmacokinetic parameters following single oral administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to sequential administration of Epivir® and Ziagen® are summarized in the table below.

PK Parameter	Geometric LS Mean[a]		Ratio of Geometric LS Means A/B	90% CI
	Treatment A N=25	Treatment B N=25		
Abacavir				
AUC_{last} (ug*h/mL)	14.12	14.12	1.000	0.955-1.048
AUC_{∞} (ug*h/mL)	14.15	14.15	1.000	0.954-1.048
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Treatment C = Fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed
a based on log-transformed data.

The plasma PK parameters t_{max} and $t_{½}$ for both ABC and 3TC were generally similar following administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to administration of the individual Epivir® and Ziagen® tablets.

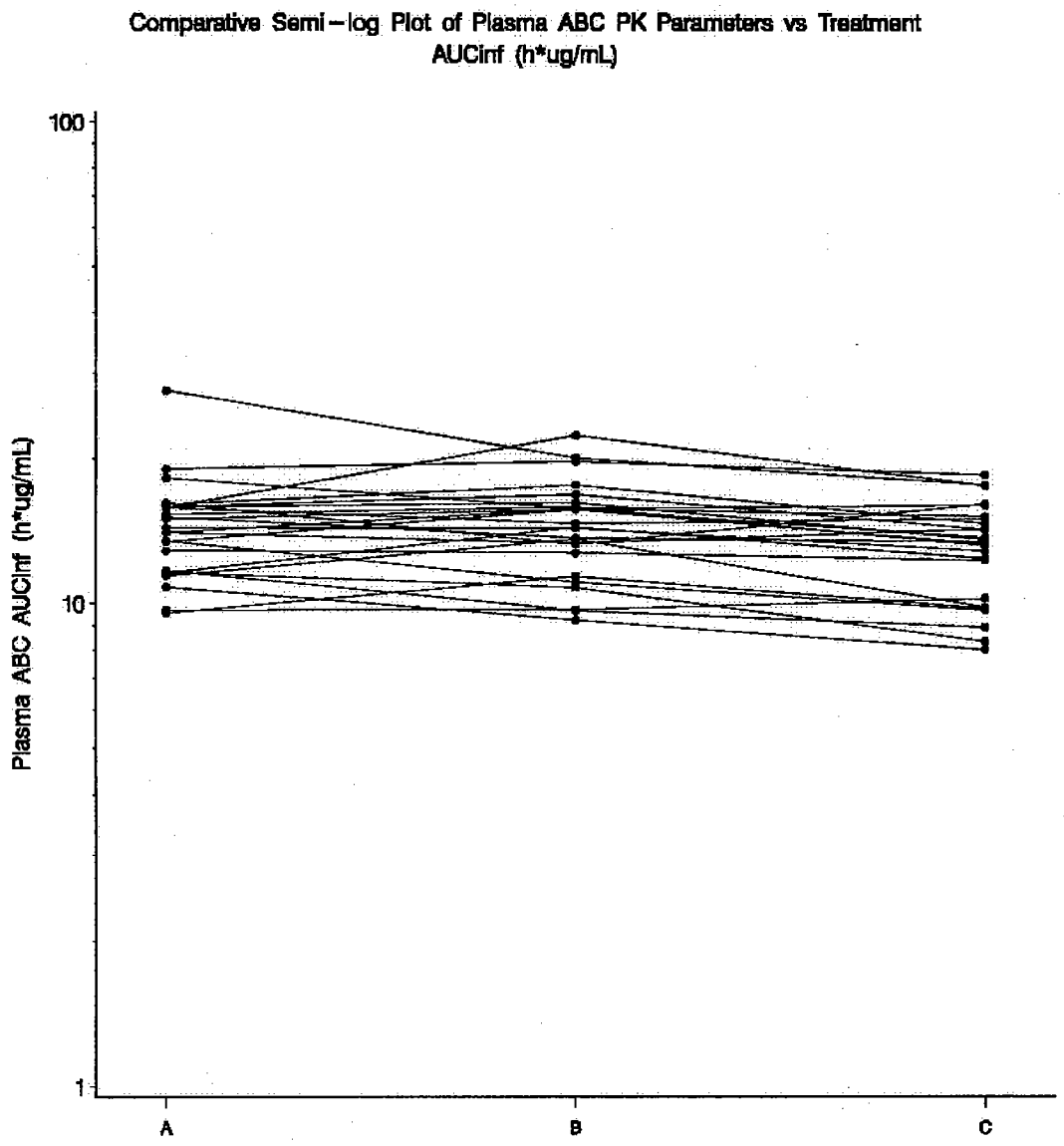
For the food effect analysis, when the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) was administered with a standard (high fat) breakfast, ABC AUClast and AUC∞ were unchanged compared to administration in the fasted state. However, ABC Cmax was decreased by approximately 24% with food. The 90% confidence intervals for the ratio (Treatment C: Treatment A) of the geometric LS means for AUClast, AUC∞ and Cmax of 3TC were completely contained within the predefined equivalence range of 0.80-1.25. Abacavir (ABC) and Lamivudine (3TC) pharmacokinetic parameters following single oral administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) fed compared to administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) fasted are summarized in the table below.

PK Parameter	Geometric LS Mean[a]		Ratio of Geometric LS Means C/A	90% CI
	Treatment A N=25	Treatment C N=25		
Abacavir				
AUC_{last} (ug*h/mL)	14.12	12.74	0.902	0.861-0.945
AUC_{∞} (ug*h/mL)	14.15	12.79	0.903	0.862-0.947
C_{max} (ug/mL)	4.68	3.54	0.757	0.684-0.838
Lamivudine				
AUC_{last} (ug*h/mL)	12.36	11.89	0.962	0.920-1.006
AUC_{∞} (ug*h/mL)	12.60	12.13	0.963	0.922-1.005
C_{max} (ug/mL)	2.64	2.27	0.860	0.800-0.924

Treatment A = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fasted
Treatment B = **ZIAGEN** (2 x 300 mg) + **EPIVIR** (2 x 150 mg) Fasted
Treatment C = fixed dose combination of abacavir/lamivudine (600 mg/300 mg) Fed
a based on log-transformed data.

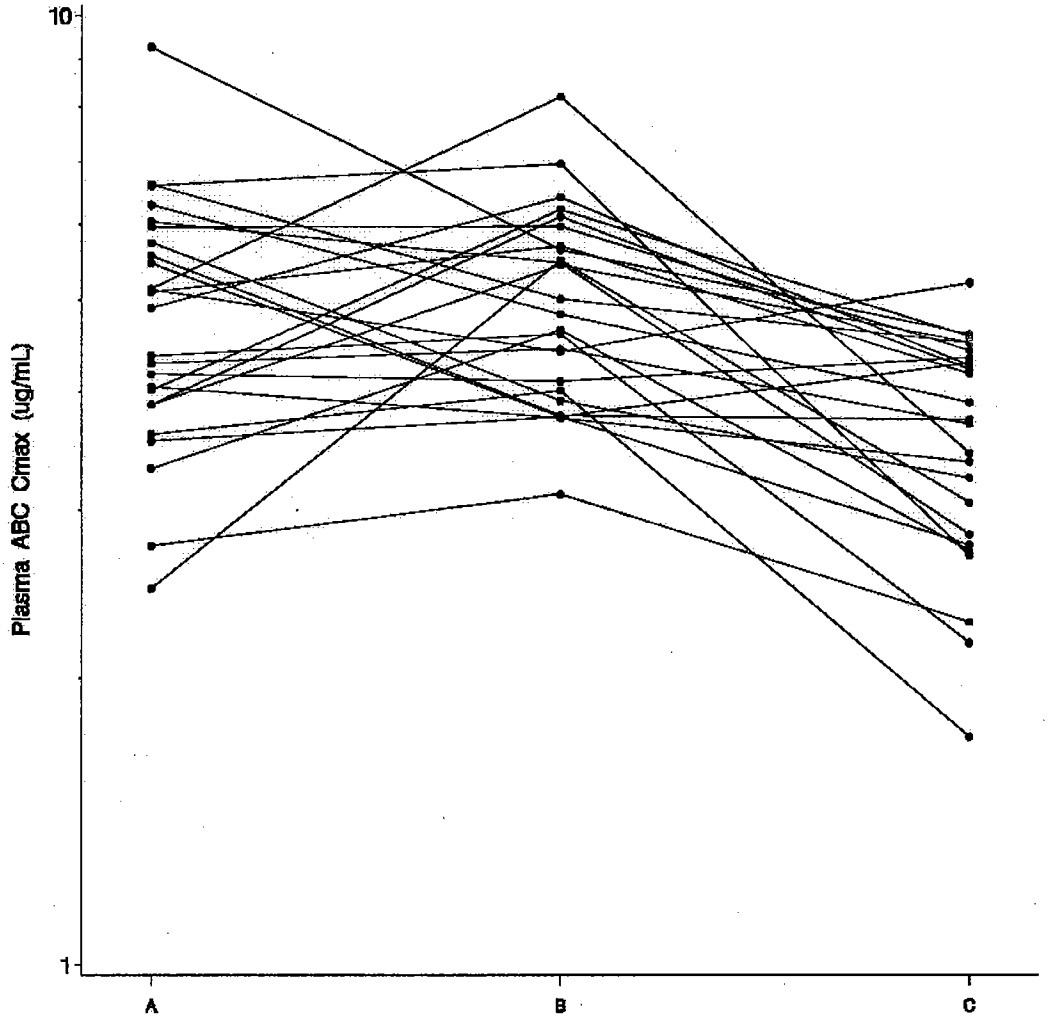
The time to peak concentration was delayed with food, and was extended by approximately 1-1.5 hours for both abacavir and lamivudine. The data show concomitant administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) with food did not alter the rate or extent of exposure of lamivudine based on AUClast, AUC∞ and Cmax data. For abacavir, administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) with food did not alter the extent of systemic exposure (based on AUClast and AUC∞), but caused a decrease in the rate of bioavailability (Cmax was decreased approximately 24%). These results are similar to those from previous studies of the effect of food on ABC and 3TC tablets given separately. Both ABC and 3TC can be given with or without food, and thus ABC/3TC can be given with or without food.

The following figures show the stickplot of AUC and Cmax of ABC and 3TC.



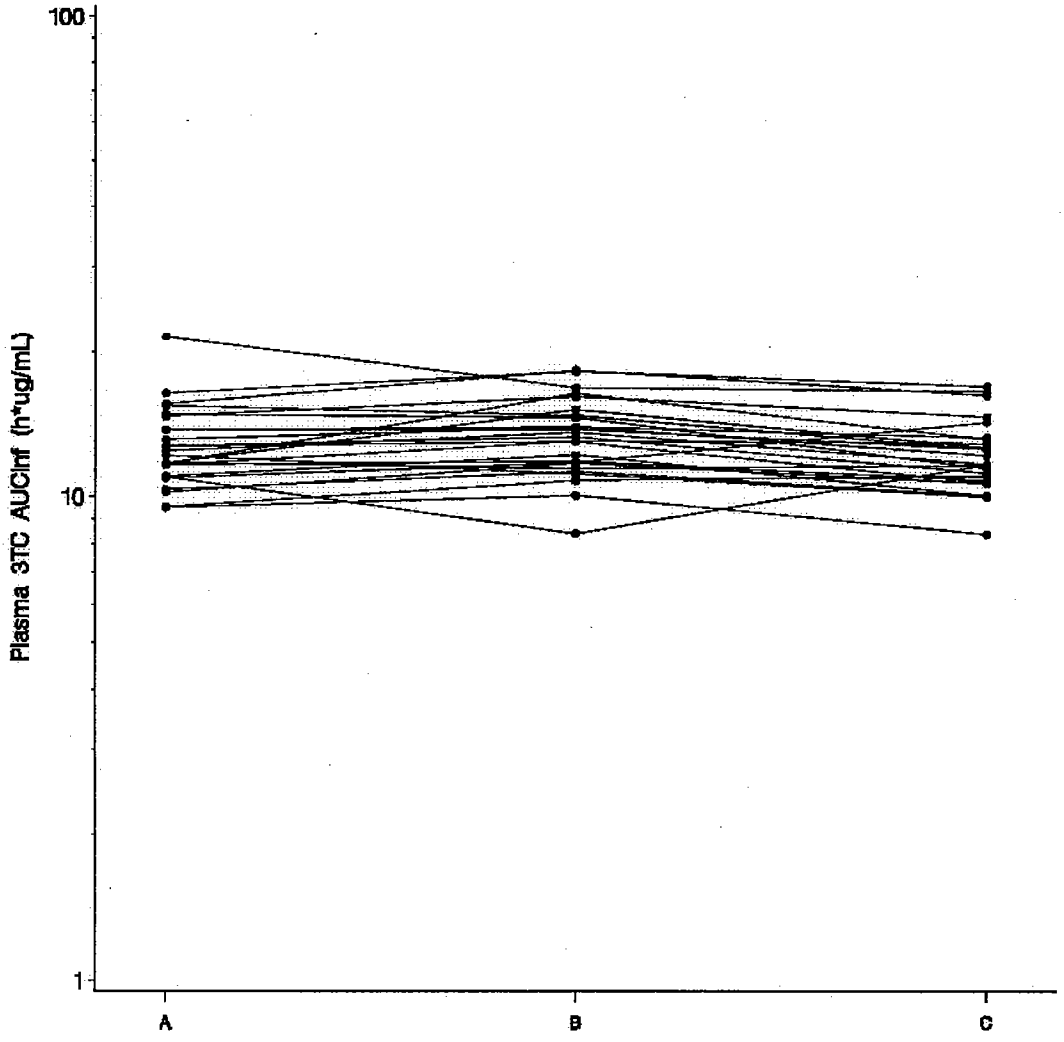
Treatment A = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fasted
Treatment B = ZIAGEN (abacavir) 2X300 mg and EPIVIR (lamivudine) 2X150 mg Fasted
Treatment C = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fed

Comparative Semi−log Plot of Plasma ABC PK Parameters vs Treatment
Cmax (ug/mL)



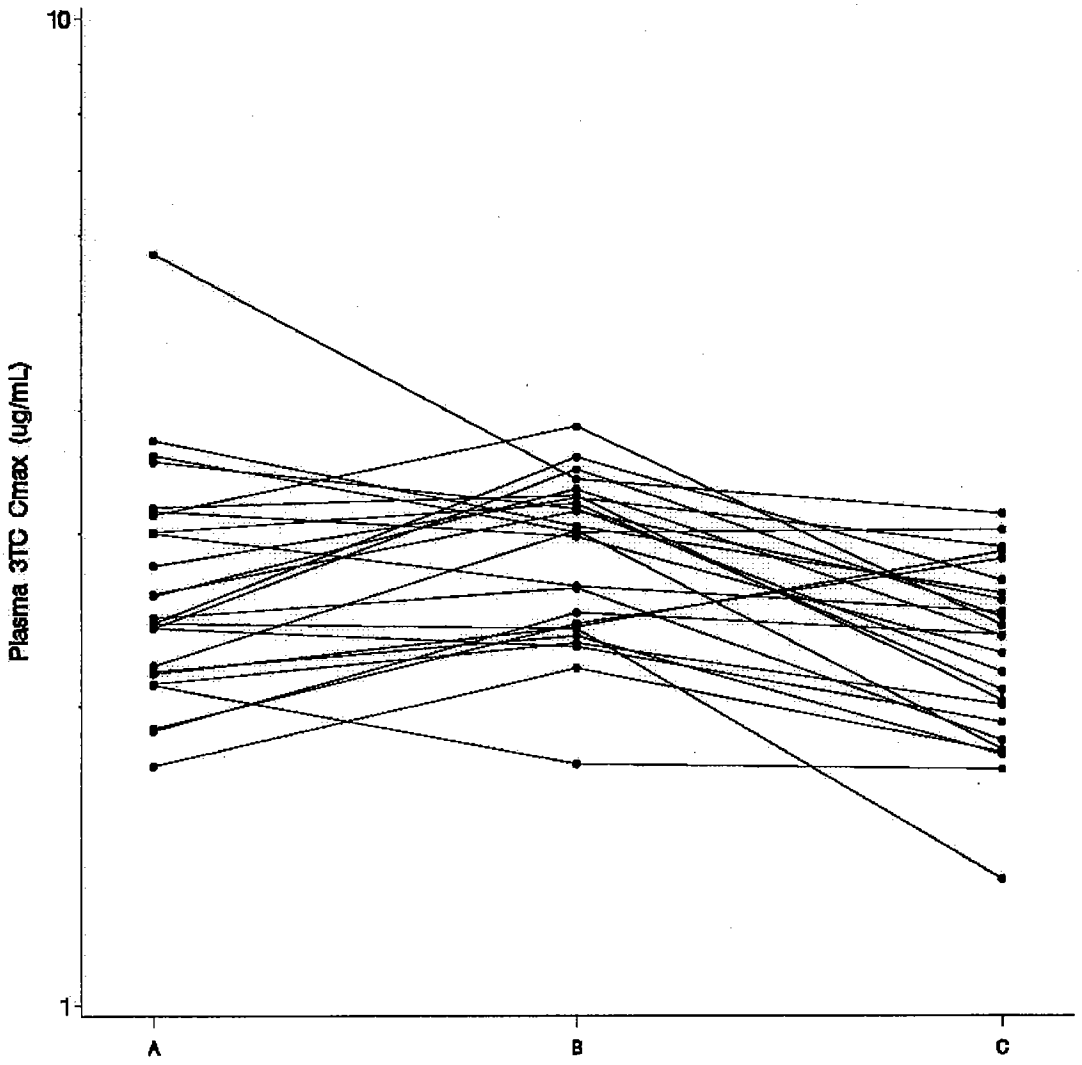
Treatment A = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fasted
Treatment B = ZIAGEN (abacavir) 2X300 mg and EPIVIR (lamivudine) 2X150 mg Fasted
Treatment C = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fed

Comparative Semi-log Plot of Plasma 3TC PK Parameters vs Treatment
AUCinf (h*ug/mL)



Treatment A = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fasted
Treatment B = ZIAGEN (abacavir) 2X300 mg and EPIVIR (lamivudine) 2X150 mg Fasted
Treatment C = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fed

Comparative Semi-log Plot of Plasma 3TC PK Parameters vs Treatment
Cmax (ug/mL)



Treatment A = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fasted
Treatment B = ZIAGEN (abacavir) 2X300 mg and EPIVIR (lamivudine) 2X150 mg Fasted
Treatment C = Combination Tablet (abacavir 600mg, lamivudine 300mg) Fed

Conclusion:

1. Bioequivalence was achieved for both abacavir and lamivudine following coadministration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) compared to sequential administration of the currently marketed products Epivir® and Ziagen®.
2. Following administration of the fixed dose combination of abacavir/lamivudine (600 mg/300 mg) in the fed state, a lack of effect of food on the rate and extent of bioavailability of lamivudine was demonstrated. The extent of bioavailability of

abacavir was unaffected in the fed state, compared to the fasted state, but the Cmax was reduced. These results are similar to those from previous studies of the effect of food on ABC and 3TC tablets given separately. Both ABC and 3TC can be given with or without food, and thus ABC/3TC can be given with or without food.

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/s/

Jenny H. Zheng
8/2/04 01:15:24 PM
BIOPHARMACEUTICS

Kellie Reynolds
8/2/04 01:25:18 PM
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