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Study No: AZL10001	
Title : An Evaluation of the Bioequivalence of a Combined Formulated Tablet (300/150/300mg abacavir/lamivudine/zidovudine) Compared to ZIAGEN (abacavir) 300mg tablet, EPIVIR (lamivudine) 150mg tablet, and RETROVIR (zidovudine) 300mg tablet Administered Concurrently and the Effect of Food on Absorption in Healthy Volunteers	
Rationale: A significant problem in treating Human Immunodeficiency Virus (HIV) infected subjects is the complexity of the combination regimens, as well as the potentially large number of concomitant medications required for the subjects' therapy. The typical standard regimen consists of greater than 10 tablets a day. Subject acceptance and adherence to such regimens is often problematic and may result in missed doses, which may decrease the efficacy of the regimen. Thus, the compactness of the triple nucleoside regimen of abacavir (ABC), lamivudine (3TC), and zidovudine (ZDV) offers advantages in pill burden and frequency that may increase adherence for those subjects in whom this regimen is appropriate. Although the triple nucleoside tablet regimen is already quite compact, further improvement in subject compliance and acceptance may be gained by reducing the pill burden for subjects. The proposed ABC/3TC/ZDV (300mg/150mg/300mg) combination tablet will further decrease pill burden.	
Phase: I	
Study Period: 16 June 1999 – 29 June 1999	
Study Design: This was a randomized, open-label, three-way crossover study.	
Centres: 1 centre in the United States	
Indication: None	
Treatment: All subjects who completed the screening were allocated to receive the three treatments in a randomized, balance fashion. The subjects were admitted as inpatients and received each treatment and a 24-hour pharmacokinetic (PK) sampling followed by a 72-hour washout period. The three treatments were: Treatment A – triple combination tablet containing ABC 300mg, 3TC 150mg, and ZDV 300mg following an overnight fast; Treatment B – ABC 300mg tablet, 3TC 150mg tablet, and ZDV 300mg tablet, swallowed sequentially following an overnight fast; and Treatment C – triple combination tablet containing ABC 300mg, 3TC 150mg, and ZDV 300mg five minutes following a standardized (high fat) breakfast. Total time in the study was 10 days.	
Objectives: The primary objective of this study was to demonstrate the bioequivalence between a single tablet composed of 300mg ABC, 150mg 3TC, and 300mg ZDV, versus the treatment with ABC 300mg, 3TC 150mg, and ZDV 300mg tablet swallowed sequentially.	
Statistical Methods: The safety population consisted of all subjects who received at least one dose of study drug. The PK population consisted of all subjects who received at least one dose of study drug and had at least one completed PK profile and produced evaluable data. The primary analysis of AUC _{last} , AUC _∞ , C _{max} , λ _z , t _{1/2} , were performed after loge-transformation. A secondary analysis was done for untransformed data. Analysis of variance (ANOVA) considering sequence, period and treatment as fixed effects and subject-within-sequence as the random effect was performed. The geometric least-square mean and 95% confidence intervals (CIs) were calculated for each treatment with their descriptive summary statistics. Two one-sided tests (90% CIs) were performed to compare AUC _{last} , AUC _∞ , C _{max} , and λ _z for Treatment A vs Treatment B and Treatment C vs Treatment A. Treatments were considered bioequivalent with respect to C _{max} and AUC if the resultant 90% confidence interval ratio falls entirely within the acceptance region of 0.80 to 1.25 for the logarithmic transformed parameters. The t _{max} data were analyzed on a pairwise basis using a Wilcoxon signed rank test ignoring periods. Estimations of the median difference between treatments and 90% CIs were calculated based on standard non-parametric methods.	
Study Population: Healthy male or female subjects, aged 18 to 55 years, who were between 50-100kg and within 25% of their ideal body weight for his/her height and frame size were eligible for this study. Additionally female subjects must have been of non-childbearing potential, or agreed to an approved method of prevention to be eligible for this study. Subjects were excluded from the study if they were HIV-positive, had a history of hypersensitivity to a study drug, had donated blood or had other significant blood loss 30 days preceding the screening phase of the study, had participated in other drug trial(s) in 30 days preceding the screening phase of the study, were actively abusing or had unexplained presence of one or more drugs of abuse, had a clinically significant finding at screening electrocardiogram, or tested positive for Hepatitis C virus antibody or Hepatitis B antigen at screening.	
Number of Subjects	Treated

Planned, N	24		
Dosed, N	24		
Completed, n (%)	24		
Total Number Subjects Withdrawn, N (%)	0		
Withdrawn due to Adverse Events, n (%)	0		
Withdrawn due to Lack of Efficacy, n (%)	Not applicable		
Withdrawn for Other Reasons, n (%)	0		
Demographics:	Treated N=24		
Females: Males	9:15		
Mean Age (sd)	37.6 (9.6)		
Mean Weight in kg (sd)	71.4 (8.8)		
White, n (%)	13 (54)		
PK Endpoints (PK Population):			
Derived ABC PK Parameters	Treatment A N=24	Treatment B N=24	Treatment C N=24
AUC _{last} (h.µg/mL)			
Geometric Mean	6.77	6.83	6.17
95% CI	5.81, 7.90	5.84, 7.99	5.41, 7.05
AUC _∞ (h.µg/mL)			
Geometric Mean	6.87	6.92	6.27
95% CI	5.89, 8.00	5.92, 8.09	5.49, 7.15
C _{max} (µg/mL)			
Geometric Mean	3.10	3.10	2.12
95% CI	2.69, 3.58	2.75, 3.51	1.79, 2.51
t _{1/2} (h)			
Geometric Mean	1.58	1.57	1.86
95% CI	1.37, 1.83	1.36, 1.82	1.61, 2.14
λ _z (1/h)			
Geometric Mean	0.438	0.440	0.373
95% CI	0.379, 0.506	0.381, 0.509	0.324, 0.430
T _{max} (h)			
Median	0.75	0.75	2.00
Range	0.50, 3.00	0.25, 2.00	0.75, 4.00
Derived 3TC PK Parameters	Treatment A N=24	Treatment B N=24	Treatment C N=24
AUC _{last} (h.µg/mL)			
Geometric Mean	5.76	6.09	5.33
95% CI	5.23, 6.35	5.43, 6.82	4.83, 5.89
AUC _∞ (h.µg/mL)			
Geometric Mean	5.92	6.23	5.47
95% CI	5.39, 6.50	5.57, 6.97	4.97, 6.03
C _{max} (µg/mL)			
Geometric Mean	1.49	1.66	1.22
95% CI	1.30, 1.72	1.41, 1.94	1.09, 1.37
t _{1/2} (h)			
Geometric Mean	6.16	6.05	5.57
95% CI	5.40, 7.02	5.49, 6.67	5.10, 6.09
λ _z (1/h)			
Geometric Mean	0.113	0.115	0.124
95% CI	0.099, 0.128	0.104, 0.126	0.114, 0.136
T _{max} (h)			
Median	1.25	1.00	2.50
Range	0.75, 3.00	0.75, 4.00	1.00, 4.00

Derived ZDV PK Parameters	Treatment A N=24	Treatment B N=24	Treatment C N=24
AUClast (h.µg/mL)			
Geometric Mean	1.96	2.06	1.98
95% CI	1.72, 2.23	1.82, 2.34	1.78, 2.19
AUC∞ (h.µg/mL)			
Geometric Mean	1.97	2.08	1.99
95% CI	1.74, 2.25	1.83, 2.36	1.80, 2.21
Cmax (µg/mL)			
Geometric Mean	1.24	1.29	0.89
95% CI	1.04, 1.48	1.07, 1.56	0.74, 1.08
t1/2 (h)			
Geometric Mean	2.40	2.21	2.48
95% CI	2.12, 2.71	1.96, 2.49	2.16, 2.85
λz (1/h)			
Geometric Mean	0.289	0.314	0.279
95% CI	0.256, 0.326	0.279, 0.353	0.243, 0.321
Tmax (h)			
Median	0.75	0.75	1.50
Range	0.50, 3.00	0.25, 2.00	0.50, 4.00
Bioequivalence Test Results: Treatment A vs Treatment B	ABC N=24	3TC N=24	ZDV N=24
AUClast (h.µg/mL)			
Geometric Least Square Mean Ratio	0.99	0.95	0.95
90% CI	0.95, 1.03	0.90, 0.99	0.88, 1.02
AUC∞ (h.µg/mL)			
Geometric Least Square Mean Ratio	0.99	0.95	0.95
90% CI	0.96, 1.03	0.91, 0.99	0.89, 1.02
Cmax (µg/mL)			
Geometric Least Square Mean Ratio	1.00	0.90	0.96
90% CI	0.90, 1.11	0.82, 0.99	0.80, 1.15
t1/2 (h)			
Geometric Least Square Mean Ratio	1.01	1.02	1.09
90% CI	0.90, 1.13	0.92, 1.12	0.94, 1.25
λz (1/h)			
Geometric Least Square Mean Ratio	0.99	0.98	0.92
90% CI	0.89, 1.12	0.89, 1.08	0.80, 1.06
Tmax (h)			
Median Difference Ratio	0.13	0.13	0.00
90% CI	0.00, 0.38	-0.13, 0.25	-0.23, 0.13
Bioequivalence Test Results: Treatment C vs Treatment A	ABC N=24	3TC N=24	ZDV N=24
AUClast (h.µg/mL)			
Geometric Least Square Mean Ratio	0.91	0.93	1.01
90% CI	0.88, 0.95	0.88, 0.97	0.94, 1.08
AUC∞ (h.µg/mL)			
Geometric Least Square Mean Ratio	0.91	0.92	1.01
90% CI	0.88, 0.95	0.88, 0.97	0.94, 1.08
Cmax (µg/mL)			
Geometric Least Square Mean Ratio	0.68	0.82	0.72
90% CI	0.62, 0.76	0.75, 0.90	0.60, 0.87
t1/2 (h)			
Geometric Least Square Mean Ratio	1.17	0.90	1.03
90% CI	1.04, 1.32	0.82, 1.00	0.90, 1.19

λ_z (1/h)			
Geometric Least Square Mean Ratio	0.86	1.08	0.98
90% CI	0.76, 0.95	0.99, 1.17	0.84, 1.11
Tmax (h)			
Median Difference Ratio	0.98	1.00	0.86
90% CI	0.63, 1.25	0.75, 1.38	0.61, 1.13
Safety Results: Safety was assessed by monitoring adverse events (AE)s, vital signs, 12-lead electrocardiogram, physical examinations, pregnancy tests, and clinical laboratory assessments.			
Most Frequent Adverse Events – On-Therapy (Safety Population), n>2	Treatment A	Treatment B	Treatment C
N	24	24	24
	n (%)	n (%)	n (%)
Subjects with any AE(s), n (%)	3 (13)	2 (8)	1 (4)
Back Pain	2 (8)	0	0
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: (Safety Population)	Treatment A N=24	Treatment B N=24	Treatment C N=24
Subjects with any SAEs, n (%) -Includes both fatal and non-fatal events	0	0	0

Conclusion:

See publication below

Publications:

Yuen GJ, Lou Y, Thompson NF, Otto VR, Allsup TL, Mahony WB, Hutman HW Abacavir/lamivudine/zidovudine as a combined formulation tablet: bioequivalence compared with each component administered concurrently and the effect of food on absorption. J Clin Pharmacol. 2001 Mar;41(3):277-88.

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