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Study No: AZL10002	
Title: An Evaluation of the Steady-State Pharmacokinetics of abacavir, lamivudine, and zidovudine following administration of a Combined Formulated Tablet (300/150/300mg abacavir/lamivudine/zidovudine) versus ZIAGEN (300mg abacavir) and COMBIVIR (150/300mg lamivudine/zidovudine) in Subjects with HIV-1 Infection.	
Rationale: Triple nucleoside therapy consisting of 300mg abacavir (ABC)/150mg lamivudine (3TC)/300mg zidovudine (ZDV) tablets twice daily or with 300mg ABC and 150mg 3TC/300mg ZDV twice daily have been studied in clinical trials for the treatment of human immunodeficiency virus (HIV) infection. These studies have demonstrated the efficacy and safety of this triple nucleoside reverse transcriptase inhibitor treatment option and may serve to preserve protease inhibitor and non-nucleoside reverse transcriptase agents for future treatment options. This regimen has some advantages over other accepted treatment regimens in reducing both frequency of dosing and pill burden over the standard two nucleoside and a protease containing regimen. Although, this treatment regimen is already quite compact, further improvement in subject compliance and acceptance may be gained by reducing the pill burden for subjects. A combined formulated tablet composed of ABC/3TC/ZDV has been developed to offer subjects convenience of a single combination tablet regimen rather than consuming single tablets of each anti-retroviral. To obtain pharmacokinetic (PK) data in HIV infected subjects, the steady state PK of ABC, 3TC, and ZDV were evaluated following administration of 3TC/ADV plus ABC versus the triple combination tablet in an observation study.	
Phase: I	
Study Period: 9 September 1999 – 30 September 1999	
Study Design: This was an open-label, multiple doses, descriptive study.	
Centres: 2 centres in France	
Indication: Human Immunodeficiency Virus	
Treatment: Subjects successfully completing screening received the following two treatments: Treatment 1 – 150mg 3TC/300mg ZDV and 300mg ABC twice daily; and Treatment 2 – triple combination tablet 300mg ABC/150mg 3TC/300mg ZDV twice daily for at least seven days. Subjects switched to the triple combination tablet after all samples for PK after treatment 1 were drawn. The duration of the study was approximately 10 days.	
Objectives: The objectives of this study were 1) to examine the PK of ABC, 3TC, ZDV at steady-state following administration of a single tablet formulation composed of 300mg ABC, 150mg 3TC, and 300mg ZDV versus the treatment of 300mg ABC and the combination tablet 150mg 3TC + 300mg ZDV in HIV infected subjects and 2) to evaluate the safety and tolerance of the combination of 3TC/ZDV and ABC, and the triple combination tablet of ABC/3TC/ZDV.	
Statistical Methods: The Safety population contained all subjects included in the study who received at least one dose of the triple combination tablet. The PK Population contained all subjects who had evaluable PK parameters. The geometric mean of each PK parameter and 95% confidence intervals (CI)s were calculated for both treatments with their descriptive summary statistics. No formal statistical comparison between the two treatment groups was made.	
Study Population: Male or female subjects, aged 18 years or older, who were HIV-1 positive, weighed between 45-100kg and within 15% of their ideal body weight for his or her height and frame size, and were receiving an antiretroviral therapy including ZDV/3TC and ABC for a minimum of two weeks prior to the study were eligible for this study. Additionally, female subjects had to have been of non-childbearing potential or have had a negative pregnancy test at screening and during the study and agreed to use an adequate and reliable form of contraception starting at least one month prior to the study drug administration and continuing throughout the study period to be eligible for this study. Subjects were excluded from the study if they had a hypersensitivity to any of the study drugs, were actively abusing or had unexplained presence of one or more drugs of abuse, had a preceding illness, had a significant existing medical condition, were using over-the-counter drugs chronically, or had difficulty abstaining from food and beverages containing caffeine and other xanthenes during their stay at the Unit.	
Number of Subjects	Treated
Planned, N	12
Dosed, N	12
Completed, n (%)	12
Total Number Subjects Withdrawn, N (%)	0
Withdrawn due to Adverse Events, n (%)	0

Withdrawn due to Lack of Efficacy, n (%)	0	
Withdrawn for Other Reasons, n (%)	0	
Demographics:	Treated N=12	
Females:Males	0:12	
Mean Age (sd)	40.8 (10.8)	
Mean Weight in kg (sd)	73.4 (11.6)	
White, n (%)	12 (100)	
PK Endpoints (PK Population):		
Summary of ABC PK Parameters	Treatment 1 N=12	Treatment 2 N=12
Cmax-ss (µg/L)		
Mean (sd)	3468.58 (1736.64)	3492.75 (1576.51)
% Coefficient Variation	50.1	45.1
Geometric Mean	3189.99	3092.93
95% CI	2470.16, 4119.60	2178.29, 4391.61
Tmax-ss (h)		
Median (Range)	0.75 (0.25, 1.50)	0.75 (0.50, 1.50)
AUCss (h. µg/L)		
Mean (sd)	6110.17 (1718.49)	6387.83 (1996.82)
% Coefficient Variation	28.1	31.3
Geometric Mean	5867.30	6084.20
95% CI	4826.73, 7132.20	4916.44, 7529.34
Lambda-z (1/h)		
Mean (sd)	0.4515 (0.1123)	0.4288 (0.1427)
% Coefficient Variation	24.9	33.3
Geometric Mean	0.4401	0.4112
95% CI	0.3803, 0.5094	0.3421, 0.4944
t1/2 (h)		
Mean (sd)	1.61 (0.35)	1.75 (0.45)
% Coefficient Variation	21.7	25.7
Geometric Mean	1.58	1.69
95% CI	1.36, 1.82	1.40, 2.03
CL/F (L/h)		
Mean (sd)	53.52 (18.00)	52.05 (19.18)
% Coefficient Variation	33.6	36.9
Geometric Mean	51.13	49.30
95% CI	42.06, 62.15	39.83, 61.02
Vss/F (L)		
Mean (sd)	119.03 (26.66)	124.24 (33.56)
% Coefficient Variation	22.4	27.0
Geometric Mean	116.17	119.90
95% CI	100.16, 134.75	100.09, 143.63
Summary of 3TC PK Parameters	Treatment 1 N=12	Treatment 2 N=12
Cmax-ss (µg/L)		
Mean (sd)	1455.67 (399.05)	1332.58 (441.40)
% Coefficient Variation	27.4	33.1
Geometric Mean	1403.45	1263.37
95% CI	1169.01, 1684.91	1012.14, 1576.95
Tmax-ss (h)		
Median (Range)	1.24 (0.50, 3.00)	1.50 (0.75, 6.00)
AUCss (h. µg/L)		
Mean (sd)	5762.75 (1780.68)	5734.25 (1789.67)
% Coefficient Variation	30.9	31.2

Geometric Mean	5530.21	5507.10
95% CI	4583.50, 6672.45	4571.08, 6634.79
CL/F (L/h)		
Mean (sd)	28.18 (7.78)	28.29 (8.23)
% Coefficient Variation	27.6	29.1
Geometric Mean	27.13	27.22
95% CI	22.48, 32.73	22.60, 32.79
Summary of ZDV PK Parameters	Treatment 1 N=12	Treatment 2 N=12
Cmax-ss (µg/L)		
Mean (sd)	1589.50 (1754.00)	1555.42 (1293.69)
% Coefficient Variation	110.3	83.2
Geometric Mean	1149.66	1193.66
95% CI	713.93 (1851.31)	748.88, 1902.60
Tmax-ss (h)		
Median (Range)	0.75 (0.25, 1.50)	0.75 (0.50, 1.00)
AUCss (h. µg/L)		
Mean (sd)	1593.92 (753.32)	1501.08 (702.98)
% Coefficient Variation	47.3	46.8
Geometric Mean	1457.12	1380.55
95% CI	1110.06, 1912.68	1063.52, 1792.09
Lambda-z (1/h)		
Mean (sd)	0.3361 (0.0467)	0.3058 (0.0552)
% Coefficient Variation	13.9	18.0
Geometric Mean	0.3332	0.3010
95% CI	0.3054, 0.3634	0.2667, 0.3397
t1/2 (h)		
Mean (sd)	2.10 (0.28)	2.35 (0.49)
% Coefficient Variation	13.5	21.0
Geometric Mean	2.08	2.30
95% CI	1.91, 2.27	2.04, 2.60
CL/F (L/h)		
Mean (sd)	222.13 (82.06)	232.54 (82.64)
% Coefficient Variation	36.9	35.5
Geometric Mean	205.90	216.93
95% CI	156.86, 270.26	167.22, 281.44
Vss/F (L)		
Mean (sd)	669.29 (256.64)	800.88 (356.87)
% Coefficient Variation	38.3	44.6
Geometric Mean	617.93	720.75
95% CI	468.40, 815.20	524.36, 990.70
Safety Results:		
Most Frequent Adverse Events – On-Therapy (Safety Population)	Treatment 1	Treatment 2
N	12	12
	n (%)	n (%)
Subjects with any AE(s), n (%)	0	6 (50)
Headaches	0	3 (25)
Nasal Inflammation	0	2 (17)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: (Safety Population)	Treatment 1 N=12	Treatment 2 N=12

Subjects with any SAEs, n (%) -Includes both fatal and non-fatal events	0	0
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Conclusion:

See publication below

Publications: Cremieux AC, Katlama C, Gillotin C, Demarles D, Yuen GJ, Raffi F; AZI10002 Study Group. A comparison of the steady-state pharmacokinetics and safety of abacavir, lamivudine, and zidovudine taken as a triple combination tablet and as abacavir plus a lamivudine-zidovudine double combination tablet by HIV-1-infected adults. *Pharmacotherapy*. 2001 Apr;21(4):424-30

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