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Study No: COD10001		
Title: A pilot open-labeled, randomized, parallel cohort, pharmacokinetic and pharmacodynamic, multicenter trial of zidovudine (<i>RETROVIR</i>) 600 mg once daily compared to zidovudine 300 mg BID monotherapy for 14 days in HIV infected, therapy naïve patients.		
Rationale: Zidovudine is currently a component of some treatment regimens for subjects with HIV infection; once daily dosing with this drug would allow physicians to tailor regimens to individual patient needs. The feasibility of dosing zidovudine once daily rests on the ability to maintain the active moiety, zidovudine triphosphate, above a minimum acceptable concentration. This is influenced by both plasma pharmacokinetics, and the intracellular zidovudine triphosphate rates of formation and elimination. Several studies suggest that early changes in viral dynamics may provide useful insight in the potential difference between various drug doses and regimens for dose selection in phase III studies. In the two-week timeframe of this study in subjects with CD4+ cell counts \geq 300 cells/ μ L who have virus with no detectable ZDV resistance mutations at screening (by RT-PCR), development of phenotypic or genotypic resistance to ZDV would be highly unlikely. This study examined the use of changes in viral dynamics as a pilot proof of concept for the use of ZDV 600 mg once daily.		
Phase: I		
Study Period: 26 February 2002 – 02 December 2002		
Study Design: Pilot open-labeled, randomized, parallel cohort, pharmacokinetic and pharmacodynamic, multicenter trial		
Centres: Eight clinical sites in the US and Puerto Rico		
Indication: HIV-1		
Treatment: Subjects were assigned to one of the following treatment groups in a randomized, balanced fashion (1:1), using a random code: ZDV 600 mg (2x 300 mg tablets), once daily x 14 days ZDV 300 mg tablet, twice daily x 14 days		
Objectives: The primary objective was: To compare the rate of HIV-1 RNA decline following the administration of zidovudine (ZDV) either as 600 mg once daily or 300 mg twice daily.		
Statistical Methods: Primary Comparisons of Interest: A daily HIV-1 RNA sample was collected from each subject during the 14-day study. HIV-1 RNA data were log ₁₀ -transformed prior to the analyses and these data were fitted with linear regression line for each treatment. The estimated slopes and difference between the slopes for plasma HIV-1 RNA were provided with 95% CI. The plasma HIV-1 RNA change from baseline was summarized by treatment and day. The proportion of subjects who achieved 0.5 log ₁₀ drop in HIV-1 RNA at each day was summarized by treatment. Other Comparisons of Interest: ZDV plasma PK parameters and ZDV triphosphate PK parameters AUC(0-∞,ss), C _{max,ss} , t _{max,ss} , C _{12,ss} (BID regimen), C _{24,ss} (QD regimen) and t _{1/2} were calculated from the concentration data collected on Day 14. These PK parameters, except t _{max,ss} , were log _e -transformed prior to the analyses and the estimated treatment ratio between ZDV 600mg QD vs. 300mg BID were expressed on the original scale. Geometric LS mean ratio and its 90%CI were provided.		
Study Population: Subjects were HIV-infected male or female (non-childbearing potential) adults (18-55 years of age, inclusive) who were antiretroviral therapy naïve. Subjects were excluded if they had any of the following: unable to take ZDV, CD4+ cells below 300 cell/ μ L at screening, clinically significant hematologic, endocrine, cardiovascular, hepatic, renal, gastrointestinal, and/or pulmonary disorder, Concurrent therapy with hydroxyurea, mycophenolate, or ribavirin or other antiretro-viral .		
Number of Subjects:	ZDV 600 mg QD	ZDV 300 mg BID
Planned N	14	14
Dosed N	20	19
Completed n (%)	19 (95)	16 (84)
Total Number Subjects Withdrawn N (%)	1 (5)	3 (16)
Withdrawn due to lack of efficacy	0	0

Withdrawn due to adverse events	0	0	
Withdrawn for Other Reasons n (%)	1 (5)	3 (16)	
Demographics	ZDV 600 mg QD	ZDV 300 mg BID	
N (Safety Population)	20	19	
Females: Males	2 : 18	2 : 17	
Mean Age in Years (sd)	35.3 (8.9)	34.7 (8.0)	
Mean Weight in Kg (sd)	79.43 (16.23)	77.19 (12.43)	
Ethnic origin n (%)			
White	8 (40)	9 (47)	
Hispanic	6 (33)	6 (38)	
Black	5 (28)	2 (13)	
Pharmacokinetics (PK) Endpoints:			
Summary of Selected ZDV PK Parameter Estimates Geometric Mean (95% CI)			
Plasma ZDV PK Parameter	ZDV 600 mg QD (N=18)	ZDV 300 mg BID (N=16)	
AUC(0-24,ss) (µg*h/mL)	1.58 (1.27-1.96)	NA ²	
AUC(0-12,ss) (µg*h/mL)	NA	0.91 (0.63-1.31)	
C _{max,ss} (µg/mL)	0.587 (0.460-0.749)	0.305 (0.197-0.470)	
C _{12,ss} (µg/mL)	0.009 (0.008-0.010)	0.006 (0.005-0.008)	
C _{24,ss} (µg/mL)	0.003 (0.008-0.010)	NA ²	
t _{1/2} (h)	3.23 (2.87-3.63)	2.32 (2.01-2.68)	
t _{max,ss} (h) ¹	2.00 (1.98-2.17)	2.00 (1.92-5.17)	
t _{max} is median and range. NA is not applicable			
Summary of Selected Intracellular ZDV Triphosphate PK Parameter Estimates: Geometric Mean (95% CI)			
Intracellular ZDV triphosphate PK Parameter	ZDV 600 mg QD (N=18)	ZDV 300 mg BID (N=16)	
AUC(0-24,ss) (fmol*h/10 ⁶ cells)	365.37 (281.48-474.25)	NA ²	
AUC(0-12,ss) (fmol*h/10 ⁶ cells)	NA ²	312.04 (244.60-398.08)	
C _{max,ss} (fmol/10 ⁶ cells)	36.743 (27.978-48.254)	43.755 (35.014-54.679)	
C _{12,ss} (µg/mL)	13.840 (9.938-19.275)	15.702 (9.460-26.065)	
C _{24,ss} (µg/mL)	5.784 (3.890-8.600)	NA ²	
t _{1/2} (h)	6.93 (6.34-7.57)	5.48 (4.02-7.45)	
t _{max,ss} (h) ¹	2.00 (1.98-8.00)	4.00 (1.92-12.00)	
t _{max} is median and range. NA is not applicable			
Plasma ZDV PK Treatment Comparisons			
Plasma ZDV PK Parameter	GLS Mean		GLS Mean Ratio (90% CI)
	ZDV 600 mg QD (N=18)	ZDV 300 mg BID (N=16)	ZDV 600 mg QD / ZDV 300 mg BID
AUC(0-24,ss) (µg*h/mL)	1.58	1.82	0.869 (0.624-1.210)
C _{max,ss} (µg/mL)	0.59	0.30	1.927 (1.311-2.834)
t _{1/2} (h)	3.23	2.32	1.391 (1.200-1.613)
t _{max} (h) ¹	2.02	2.34	0.863 (0.709-1.017)
median difference (90% CI) for comparison for t _{max} .			
Intracellular ZDV Triphosphate PK Treatment Comparisons			
Plasma ZDV PK Parameter	GLS Mean		GLS Mean Ratio (90% CI)
	ZDV 600 mg QD (N=18)	ZDV 300 mg BID (N=16)	ZDV 600 mg QD / ZDV 300 mg BID

AUC(0-24,ss) (fmol*h/10 ⁶ cells)	365.37	624.08	0.585 (0.439-0.780)			
C _{max,ss} (fmol/10 ⁶ cells)	36.74	43.76	0.840 (0.631-1.118)			
t _{1/2} (h)	6.93	5.48	1.265 (1.008-1.588)			
t _{max} (h) ¹	2.91	4.33	0.670 (0.369-0.972)			
median difference (90% CI) for comparison for t _{max}						
Pharmacodynamics (PD) Endpoints:						
Summary of Plasma HIV-1 RNA Mean and Median (Range) Change from Baseline by Treatment (copies/mL)						
Study Day	ZDV 600 mg QD N=18			ZDV 300 mg BID N=16		
	n	Mean (SD)	Median (Min, Max)	n	Mean (SD)	Median (Min, Max)
Day 2	18	-0.044 (0.211)	-0.010 (-0.447, 0.304)	16	-0.123 (0.224)	-0.162 (-0.434, 0.387)
Day 4	16	-0.340 (0.192)	-0.346 (-0.747, 0.137)	16	-0.431 (0.191)	-0.398 (-0.723, -0.096)
Day 6	18	-0.494 (0.250)	-0.476 (-0.949, -0.067)	16	-0.647 (0.352)	-0.619 (-1.796, -0.321)
Day 8	18	-0.633 (0.302)	-0.547 (-1.180, -0.162)	16	-0.655 (0.242)	-0.576 (-1.222, -0.326)
Day 10	18	-0.592 (0.267)	-0.524 (-1.271, -0.249)	16	-0.630 (0.302)	-0.548 (-1.254, -0.275)
Day 12	18	-0.557 (0.327)	-0.451 (-1.217, -0.008)	16	-0.639 (0.409)	-0.531 (-1.426, -0.104)
Day 14	18	-0.568 (0.414)	-0.492 (-1.446, -0.073)	16	-0.638 (0.286)	-0.616 (-1.108, -0.096)
Summary of Plasma HIV-1 RNA Median Change from Baseline by Treatment and Triphosphate Concentration						
Study Day/ Median (Min, Max)	ZDV 600 mg QD N=18		ZDV 300 mg BID N=16			
	BLQ N=11	No BLQ N=7	BLQ N=4	No BLQ N=12		
Day 2	0.042 (-0.317, 0.304)	-0.190 (-0.447, 0.143)	0.086 (-0.434, 0.387)	-0.210 (-0.412, 0.086)		
Day 4	-0.311 (-0.445, 0.137)	-0.415 (-0.747, -0.218)	-0.380 (-0.723, -0.167)	-0.398 (-0.721, -0.096)		
Day 6	-0.421 (-0.949, -0.067)	-0.546 (-0.837, -0.153)	-0.428 (-0.698, -0.334)	-0.643 (-1.796, -0.321)		
Day 8	-0.449 (-1.180, -0.162)	-0.645 (-1.145, -0.444)	-0.534 (-0.912, -0.326)	-0.583 (-1.222, -0.427)		
Day 10	-0.517 (-1.271, -0.249)	-0.713 (-0.999, -0.305)	-0.501 (-1.254, -0.275)	-0.548 (-1.143, -0.323)		
Day 12	-0.393 (-1.217, -0.008)	-0.822 (-0.890, -0.410)	-0.509 (-1.272, -0.104)	-0.537 (-1.426, -0.245)		
Day 14	-0.196 (-1.192, -0.073)	-0.801 (-1.446, -0.337)	-0.647 (-1.108, -0.315)	-0.616 (-1.102, -0.096)		
BLQ = Below the limits of quantitation						
Summary of Maximum Change for Plasma HIV-1 RNA by Treatment						
	ZDV 600 mg QD N=18		ZDV 300 mg BID N=16			
Mean (SD)	-0.764 (0.340)		-0.879 (0.413)			
Median (Min, Max)	-0.624 (-1.493, -0.432)		-0.759 (-2.046, -0.379)			
Summary of the Proportion of Subjects with a >0.5 log₁₀ (copies/mL) Decline in Plasma HIV-1 RNA by Day and Treatment						

Study Day	ZDV 600 mg QD N=18	ZDV 300 mg BID N=16
	n/N (%)	n/N (%)
Day 2	0/18 (0%)	0/16 (0%)
Day 4	2/16 (13%)	6/16 (38%)
Day 6	8/18 (44%)	10/16 (63%)
Day 8	10/18 (56%)	12/16 (75%)
Day 10	10/18 (56%)	11/16 (69%)
Day 12	6/18 (33%)	9/16 (56%)
Day 14	9/18 (50%)	10/16 (63%)
Viral Genotyping and Phenotyping: No ZDV resistance mutations were observed in this study.		
Safety Results: All adverse event (AE) information was collected at each visit starting from Day 1 of the first period through to the follow-up visit. All other AEs which occurred during the screening period were recorded as current medical conditions. AEs occurring in at least two subjects in any treatment group are presented by rate of occurrence below.		
Adverse Events:	ZDV 600 mg QD	ZDV 300 mg BID
N (Safety Population)	20	19
No. subjects with AEs n (%)	18 (90)	18 (95)
Headache	10 (50)	9 (47)
Nausea	6 (30)	9 (47)
Fatigue	8 (40)	7 (37)
Diarrhea	2 (10)	3 (16)
Dizziness	3 (15)	2 (11)
Drowsiness	2 (10)	1 (5)
Lightheadedness	1 (5)	2 (11)
Vomiting	2 (10)	1 (5)
Xerostomia	2 (10)	1 (5)
Serious Adverse Events, n (%) [including both fatal and non-fatal]:	0 (0)	0 (0)

Publications: No Publication
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