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<b>Study No.:</b> AZL30006	
<b>Title:</b> A Phase IIIb/IV, Randomized, Open Label, Multicenter, Pilot Trial to Explore the Safety and Tolerability of GW433908 +/- Ritonavir (1400mg twice daily or 700mg/100mg twice daily) When Used in Combination with a Zidovudine-containing Regimen (TRIZIVIR or COMBIVIR twice daily) Over a 24 Week Period in Antiretroviral Therapy Naive HIV-1 Infected Subjects	
<b>Rationale:</b> Amprenavir (APV) is a protease inhibitor (PI) developed for the treatment of HIV disease. When given in combination with other antiretroviral agents, it requires a large pill count that may impact long term adherence to therapy. Fosamprenavir (FPV), the phosphate ester prodrug of APV, can be administered with a smaller pill count and may deliver similar antiviral efficacy and safety results. In an earlier study comparing APV + lamivudine (3TC) + zidovudine (ZDV) to placebo (PBO) + 3TC + ZDV, the overall incidence of drug-related adverse events (AEs) was statistically significantly higher in the APV regimen. Given that FPV tablets: 1) are smaller than APV capsules, 2) require a lower pill-burden, and 3) do not contain the excipients (i.e. vitamin E and propylene glycol) suspected of causing the gastrointestinal (GI) toxicity seen with APV therapy, it was hypothesized that the GI toxicity might be decreased with coadministration of FPV and ZDV. However, these improvements in the delivery of APV by FPV compared to APV could potentially be offset by a PK interaction between FPV and ZDV similar to that observed with APV and ZDV, resulting in increased ZDV levels and high rates of GI intolerance. Thus, the primary driver of this pilot trial was to assess the pharmacokinetic (PK) profile of ZDV and the safety profile of FPV, either with or without ritonavir (RTV) when co-administered with a ZDV-containing regimen.	
<b>Phase:</b> IIIb/IV	
<b>Study Period:</b> 28 June 2002 – 19 May 2003	
<b>Study Design:</b> This was a 24-week, randomized, parallel group, four-arm, open-label, multicenter, comparative study. Subjects who completed the study and elected to remain on FPV had the option of enrolling in an extension study.	
<b>Centres:</b> 10 centres in the United States, 3 centres in France	
<b>Indication:</b> Human Immunodeficiency Virus	
<b>Treatment:</b> Subjects were randomized (1:1:1:1) to the following four treatment groups:	
<b>Treatment Group</b>	<b>Study Treatment</b>
1	FPV 1400mg twice daily (BID) + TRIZIVIR [3TC 150mg/ZDV 300mg/abacavir (ABC) 300mg] (TZV) BID
2	FPV 700mg BID + RTV 100mg BID + TZV BID
3	FPV 1400mg BID + COMBIVIR [3TC 150mg/ZDV 300mg] (COM) BID
4	FPV 700mg BID + RTV 100mg BID + COM BID
Subjects participated in a screening period (up to Day -28 to Day -1), a randomized treatment period (Day 1 through Week 24), and a follow-up evaluation (performed 4 weeks after permanent discontinuation of study medication). Each subject completed the study after 24 weeks of randomized therapy and the follow-up visit. No dose reductions of any study medication(s) were allowed. Subjects requiring a disruption of any study medication more than 14 days were discontinued from the study. If a subject in Treatment Group 1 or 2 developed a hypersensitivity reaction to ABC, the subject was allowed to drop the ABC and continue in the study by substituting COM (3TC 150mg/ZDV 300mg) BID for TZV (3TC 150mg/ZDV 300mg/ABC 300mg) BID.	
All subjects enrolled in the study were to provide a plasma ZDV sample at 1-hour post-dosing on Week 1, and subjects enrolled in Treatments 3 and 4 were to provide a plasma ZDV PK sample over a 6-hour post-dosing period on Week 4. Subjects who provided Week 4 ZDV samples were asked to provide consent to allow the samples to be additionally analyzed for APV concentrations; not all subjects re-consented.	
<b>Objectives:</b>	
The primary objective of this study was to assess the overall short-term tolerance of the regimens under investigation (e.g. To assess the frequency and nature of adverse events, treatment limiting adverse events, and the time to onset of the most frequently occurring adverse events.)	
The secondary objectives of this study were:	
To assess the nature and incidence of laboratory abnormalities	
To assess the impact/burden of AEs to subjects, as measured by the Most Bothersome Adverse Events (MBAE) Questionnaire;	
To describe plasma ZDV PK following coadministration of COM (3TC 150mg/ZDV 300mg) BID and FPV 1400mg BID	

for 4 weeks;  
 To describe plasma ZDV PK following coadministration of COM (3TC 150mg/ZDV 300mg) BID and FPV 700mg BID + RTV 100mg BID for 4 weeks;  
 To describe plasma ZDV peak (1-hour) concentrations following administration of each of the four treatments;  
 To compare change from baseline in plasma HIV-1 RNA levels over time;  
 To describe plasma APV PK following coadministration of COM (3TC 150mg/ZDV 300mg) BID and FPV 1400mg BID for 4 weeks;  
 To describe plasma APV PK following coadministration of COM (3TC 150mg/ZDV 300mg) BID and FPV 700mg BID + RTV 100mg BID for 4 weeks.

**Primary Outcome/Efficacy Variable:** Safety

**Secondary Outcome/Efficacy Variable(s):** The secondary efficacy endpoints were the measured values and absolute changes from baseline in plasma HIV-1 RNA levels over time. Other efficacy endpoints included measured values and absolute changes from baseline in CD4+ cell counts over time and the occurrence of HIV-associated conditions over time.

**Statistical Methods:** The planned sample size for this study was 60 subjects. This sample size was not based on any power calculations, since being a pilot study, the analysis was hypothesis generating rather than a confirmation of any suspected hypothesis. The Intent to Treat (Exposed) [ITT(E)] and Safety Populations included all randomized subjects who received at least one dose of study medication. The Safety Population was the population used for all safety and Global Health Outcomes (GHO) analyses and subjects were analyzed according to the treatment actually received, regardless of randomization. The ITT(E) population was the population used for efficacy analyses and subjects were analyzed in the treatment group to which they were randomized. The Week 1 PK Summary Population consisted of all subjects for whom a 1-hour plasma ZDV concentration was reported. This population was used for the summary of the Week 1 1-hour plasma ZDV concentrations and the analysis of the relationship between Week 1 1-hour plasma concentrations and adverse events. The Week 4 PK Summary Population consisted of all subjects for whom a plasma ZDV or APV PK parameter was estimated on Week 4. This population was used for the individual and summary plasma ZDV and APV concentration-time profiles, the summaries of plasma ZDV and APV concentration-time data, and figures of derived plasma ZDV and APV PK parameters. The factorial design of this study facilitated two treatment comparisons of interest; ABC-containing regimens versus non-ABC containing regimens and RTV-containing regimens versus non-RTV-containing regimens. The primary analysis of interest was to present all treatment groups combined, however, selected safety analyses were presented by these comparisons and/or by treatment groups. Analyses of antiviral response included summaries of the actual values and changes from baseline in log<sub>10</sub> plasma HIV-1 RNA and CD4+ cell counts at each visit for all treatment groups combined. Values for the following plasma ZDV and APV PK parameters were estimated from Week 4 concentration data: C<sub>max</sub>; t<sub>max</sub>; the area under the plasma concentration versus time curve from 0 to 6 hours after dosing (AUC<sub>(0-6)</sub>); the area under the plasma concentration versus time curve over the dosing interval (τ) at steady-state (AUC<sub>(0-τ)</sub>); and for APV, the plasma concentration at the end of the dosing interval (τ) at steady-state (C<sub>τ</sub>). Plasma ZDV and APV PK parameter values were summarized by treatment using geometric means and 95% confidence intervals. Analysis of variance, with treatment as a fixed effect, was used to compare plasma ZDV and APV PK, and ratios of generalized least square means and associated 90% confidence intervals were estimated.

**Study Population:** Male or female subjects, aged 13 years or older (or 18 years or older according to local requirements), with screening plasma HIV-1 RNA ≥ 1,000 copies/mL and screening CD4+ cell count ≥ 100 cells/mm<sup>3</sup>, that were antiretroviral therapy naïve were eligible for this study. Additionally, female subjects had to be of non-childbearing potential or have a negative serum β-Human Chorionic Gonadotrophin (HCG) pregnancy result at screening and agreed to use a proven barrier method of contraception during the study. Hormonal contraceptives were not considered a sufficient form of contraception.

<b>Number of Subjects:</b>	<b>Treatment 1</b>	<b>Treatment 2</b>	<b>Treatment 3</b>	<b>Treatment 4</b>
Planned, N	15	15	15	15
Randomized & Treated, N	15	15	16	16
Safety Population	15	15	16	16
ITT[E] Population	15	15	16	16
PK Summary Population Week 1	9	11	14	15
PK Summary Population Week 4	Not Applicable (NA)	NA	ZDV:13 APV: 10	ZDV:12 APV: 11
Completed, n (% Randomized/Treated)	11 (73)	13 (87)	12 (75)	13 (81)
Total Number of Subjects "Missing" (% Randomized/Treated)	2 (13)	0	0	0

Total Number of Subjects Withdrawn, n (% Randomized/Treated)	2 (13)	2 (13)	4 (25)	3 (19)
Withdrawn due to Adverse Events, n (%)	1(7)	0	2(13)	0
Withdrawn due to Lack of Efficacy, (n)%	0	0	0	0
Withdrawn for other reasons, n (%)	1(7)	2(13)	2(13)	3(19)
<b>Demographics: (Safety Population)</b>		<b>All Treatments Combined N=62</b>		
Females: Males		11:51		
Mean Age, years (sd)		38.1 (11.08)		
White, n (%)		41 (66)		
<b>Primary Efficacy Results: (ITT[E] Population) - Safety – See Safety Results Below</b>				
<b>Secondary Efficacy Results: (ITT[E] Population)</b>				
<b>Median Plasma HIV-1 RNA (log<sub>10</sub> copies/ mL)</b>		<b>All Treatments Combined N=62</b>		
Baseline, n		62		
Median (Range)		4.86 (3.27, 5.87)		
Week 4, n		57		
Median (Range)		2.70 (1.69, 5.41)		
Week 12, n		52		
Median (Range)		1.87 (1.69, 5.15)		
Week 24, n		50		
Median (Range)		1.69 (1.69, 4.53)		
<b>Median Change from Baseline in HIV-1 RNA (log<sub>10</sub> copies/mL)</b>		<b>All Treatments Combined N=62</b>		
Week 4, n		57		
Median (Range)		-2.11 (-3.42, 0.21)		
Week 12, n		52		
Median (Range)		-2.95 (-3.54, 0.56)		
Week 24, n		50		
Median (Range)		-3.15 (-4.17, -0.14)		
<b>Other Efficacy Results: (ITT[E] Population)</b>				
<b>Median CD4+ Cell Count (cells/mm<sup>3</sup>)</b>		<b>All Treatments Combined N=62</b>		
Baseline, n		62		
Median (Range)		334 (72, 839)		
Week 4, n		57		
Median (Range)		427 (140, 1023)		
Week 12, n		53		
Median (Range)		464 (147, 1078)		
Week 24, n		49		
Median (Range)		449 (130, 1146)		
<b>Median Change from Baseline in CD4+ Cell Count (cells/mm<sup>3</sup>)</b>		<b>All Treatments Combined N=62</b>		
Week 4, n		57		
Median (Range)		59 (-198, 421)		
Week 12, n		53		
Median (Range)		120 (-133, 338)		
Week 24, n		49		
Median (Range)		116 (-218, 551)		
<b>HIV Associated Conditions</b>				
No subject reported any HIV-associated conditions during the study.				
<b>Safety Results:</b> Assessments for AEs were conducted at the screening visit, Day 1 and at Weeks 1, 2, 4, 8, 12, 24/Withdrawal. Only SAEs relating to study participation were collected by the investigator during the screening period (i.e., Day –28 through to Day 1). Note: NOS = Not Otherwise Specified.				
<b>Most Frequent Treatment Emergent Adverse Events – Non-</b>		<b>Treatment 3 and</b>	<b>Treatment 1 and</b>	

<b>ABC-Containing Regimens vs ABC-Containing Regimens (Safety Population)</b>	<b>Treatment 4 N=35</b>	<b>Treatment 2 N=30</b>
	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s)	30 (86)	28 (93)
Nausea	21 (60)	18 (60)
Diarrhea NOS	16 (46)	14 (47)
Rash NOS	8 (23)	5 (17)
Fatigue	7 (20)	7 (23)
Headache	7 (20)	2 (7)
Insomnia	6 (17)	6 (20)
Dyspepsia	4 (11)	5 (17)
Abdominal Pain NOS	4 (11)	1 (3)
Sinusitis NOS	4 (11)	1 (3)
Vomiting NOS	3 (9)	6 (20)
Arthralgia	3 (9)	3 (10)
Depression	3 (9)	3 (10)
Pyrexia	3 (9)	3 (10)
Anxiety	3 (9)	2 (7)
Cough	3 (9)	2 (7)
Dysgeusia	3 (9)	2 (7)
Asthenia	3 (9)	1 (3)
Dizziness	3 (9)	1 (3)
Rhinorrhea	3 (9)	1 (3)
Back Pain	3 (9)	0
Anorexia	2 (6)	5 (17)
Drug Hypersensitivity	0	3 (10)
Note: 2 subjects are included in the both "FPV+TZV" and "FPV+COM" arms and 1 subject is included in both "FPV+RTV+TZV" and "FPV+RTV+COM" arms, because they switched from TZV to COM during the treatment period.		
<b>Most Frequent Adverse Events – Non-RTV-Containing Regimens vs RTV-Containing Regimens (Safety Population)</b>	<b>Treatment 1 and Treatment 3 N=31</b>	<b>Treatment 2 and Treatment 4 N=31</b>
	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s)	27 (87)	29 (94)
Nausea	21 (68)	18 (58)
Diarrhea NOS	11 (35)	19 (61)
Rash NOS	9 (29)	4 (13)
Fatigue	8 (26)	6 (19)
Insomnia	5 (16)	7 (23)
Vomiting NOS	5 (16)	4 (13)
Headache	4 (13)	5 (16)
Arthralgia	3 (10)	3 (10)
Depression	3 (10)	3 (10)
Pyrexia	3 (10)	3 (10)
Cough	3 (10)	2 (6)
Dysgeusia	3 (10)	2 (6)
Asthensia	3 (10)	1 (3)
Dizziness	3 (10)	1 (3)
Myalgia	3 (10)	1 (3)
Rhinorrhea	3 (10)	1 (3)
Bronchitis	3 (10)	0
Abdominal pain NOS	2 (6)	3 (10)
Anxiety	2 (6)	3 (10)
Dyspepsia	2 (6)	7 (23)
Anorexia	2 (6)	5 (16)
Sinusitis NOS	1 (3)	4 (13)

Abdominal distention	0	3(10)
<b>Serious Adverse Events – Non-ABC-Containing Regimens vs ABC-Containing Regimens (Safety Population)</b> n (%) [n considered by the investigator to be related to study medication]	<b>Treatment 3 and Treatment 4</b> N=35	<b>Treatment 1 and Treatment 2</b> N=30
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Subjects with any SAE(s), n (%)	2 (6)	5 (17)
Hepatitis C	1 (3) [1]	0
Infection NOS	1 (3) [0]	0
Drug Hypersensitivity	0	3 (10) [3]
Depression	0	1 (3) [0]
Drug Dependence	0	1 (3) [0]
Asthma NOS	0	1 (3) [0]
Note: 2 subjects are included in the both “FPV+TZV” and “FPV+COM” arms and 1 subject is included in both “FPV+RTV+TZV” and “FPV+RTV+COM” arms, because they switched from TZV to COM during the treatment period.		
Subjects with fatal SAEs, n (%)	0	0
<b>Serious Adverse Events – Non-RTV-Containing Regimens vs RTV-Containing Regimens (Safety Population)</b> n (%) [n considered by the investigator to be related to study medication]	<b>Treatment 1 and Treatment 3</b> N=31	<b>Treatment 2 and Treatment 4</b> N=31
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Subjects with any SAE(s), n (%)	5 (16)	2 (6)
Drug Hypersensitivity	2 (6) [2]	1 (3) [1]
Hepatitis C	1 (3) [1]	0
Infection NOS	1 (3) [0]	0
Depression	1 (3) [0]	0
Drug Dependence	1 (3) [0]	0
Asthma NOS	0	1 (3) [0]
Subjects with fatal SAEs, n (%)	0	0
<b>PK Endpoints (PK Summary Population):</b>		
<b>PK Results Week 1:</b>		
In agreement with the Week 4 plasma ZDV PK data, the Week 1, 1-hour plasma ZDV concentrations appeared lower for the two 908FPV/RTV treatment groups (Groups 2 and 4) compared to the two 908FPV treatment groups (Groups 1 and 3). The median 1-hour plasma ZDV concentrations for each of the regimens were: Treatment 2: 0.477ug/mL; Treatment 4: 0.479ug/mL; Treatment 1: 0.628ug/mL; and Treatment 3: 0.679ug/mL.		
<b>Plasma ZDV PK Summary - Week 4 (PK Summary Population Week 4)</b>	<b>Treatment 3</b> N=13	<b>Treatment 4</b> N=12
Cmax (µg/mL) Geometric Mean (95% CI)	1.171 (0.881, 1.557)	0.911 (0.658, 1.263)
AUC(0-6) (µg.h/mL) Geometric Mean (95% CI)	1.633 (1.332, 2.002)	1.364 (0.970, 1.918)
AUC (0-τ) (µg.h/mL) Geometric Mean (95% CI)	1.754 (1.406, 2.188)	1.480 (1.025, 2.138)
tmax (h) Median (Range)	0.50 (0.48, 2.00)	1.01 (0.48, 1.52)
<b>Plasma APV PK Summary - Week 4 (PK Summary Population Week 4)</b>	<b>Treatment 3</b> N=10	<b>Treatment 4</b> N=11
Cmax (µg/mL) Geometric Mean (95% CI)	4.21 (3.02, 5.87)	5.94 (4.50, 7.83)
AUC(0-6) (µg.h/mL) Geometric Mean (95% CI)	13.46 (9.64, 18.81)	22.74 (16.51, 31.32)
AUC (0-τ) (µg.h/mL) Geometric Mean (95% CI)	17.26 (12.60, 23.64)	34.82 (24.36, 49.76)
Cτ (µg.h/mL) Geometric Mean (95% CI)	0.456 (0.280, 0.743)	1.39 (0.791, 2.42)
tmax (h) Median (Range)	1.58 (1.00, 2.00)	1.58 (1.00, 4.02)
<b>Plasma ZDV PK Treatment Comparison - Week 4</b>	<b>Geometric Least Squares (GLS) Mean</b>	
	<b>Treatment 3</b> N=13	<b>Treatment 4</b> N=12
	<b>Treatment 4 vs Treatment 3</b>	
Cmax (µg/mL)	1.17	0.91
AUC(0-6) (µg.h/mL)	1.63	1.36
	0.778 (0.555, 1.091)	
	0.835 (0.616, 1.133)	

AUC (0- $\tau$ ) ( $\mu\text{g.h/mL}$ )	1.75	1.48	0.844 (0.607, 1.172)
<b>Plasma APV PK Treatment Comparison - Week 4</b>	<b>GLS Mean</b>		<b>GLS Mean Ratio (90% CI)</b>
	<b>Treatment 3 N=10</b>	<b>Treatment 4 N=11</b>	<b>Treatment 4 vs Treatment 3</b>
C <sub>max</sub> ( $\mu\text{g/mL}$ )	4.21	5.94	1.410 (1.013, 1.961)
AUC(0-6) ( $\mu\text{g.h/mL}$ )	13.46	22.74	1.689 (1.182, 2.413)
AUC (0- $\tau$ ) ( $\mu\text{g.h/mL}$ )	17.26	34.82	2.017 (1.393, 2.922)
C $\tau$ ( $\mu\text{g.h/mL}$ )	0.46	1.38	3.038 (1.704, 5.419)
t <sub>max</sub> (h) (LS mean ratio for comparison for t <sub>max</sub> )	1.57	1.82	1.159 (0.844, 1.474)

**Conclusions:**

Substantial virologic suppression and immunologic responses were observed over 24 weeks. However, owing to the small number of subjects in the study, it was determined that analysis of antiviral response for each individual treatment group was not appropriate. Nausea, diarrhea and rash were the most frequently reported adverse events in all treatment groups. Serious adverse events were reported in 7 subjects with drug hypersensitivity being the only serious adverse event being reported by more than one subject. No deaths were reported during this study.

**Publications:** No publication

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