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<b>Study No.:</b> AZL40001
<b>Title:</b> An open-label, single arm, multicentre, pilot phase IV study to evaluate the efficacy and safety of a potent combination therapy ( <i>Trizivir</i> + Efavirenz) in antiretroviral naïve adults with a CD4+ cell count <200mm <sup>3</sup> over a 48-week treatment period (TETRA – Trizivir Efavirenz TReAtment)
<b>Rationale:</b> This study was carried out to further evaluate the anti-retroviral activity of abacavir, lamivudine, zidovudine (ABC, 3TC, ZDV) + Efavirenz in therapy naïve subjects with a CD4 count <200 cells/mm <sup>3</sup> .
<b>Phase:</b> IV
<b>Study Period:</b> 21 February 2001 to 12 December 2002
<b>Study Design:</b> Open-label, single arm, multicentre, pilot phase IV
<b>Centres:</b> 10 centres in the UK
<b>Indication:</b> HIV-1 Infection
<b>Treatment:</b> abacavir 300mg, lamivudine 150mg, zidovudine 300mg, one tablet twice a day; oral Efavirenz – 200mg capsules, 3 capsules once a day; oral Nevirapine – 200mg tablets, 1 tablet twice a day; oral
<b>Objectives: Primary:</b> To evaluate the antiretroviral activity of the quadruple therapy (ABC, 3TC, ZDV + Efavirenz) in severely immunologically suppressed HIV-1 infected subjects
<b>Primary Outcome/Efficacy Variable:</b> Percentage of subjects with plasma HIV-1 RNA concentration <50 copies/mL at weeks 24 and 48
<b>Secondary Outcome/Efficacy Variable(s):</b> Percentage of subjects achieving plasma HIV-1 RNA concentration below 3 copies/mL at weeks 24, 32, 40, and 48; plasma HIV-1 RNA over time; Log <sub>10</sub> HIV-1 RNA over time; time to obtain a HIV-1 RNA of <50 copies/mL; change in CD4+ cell count; treatment adherence and correlation with the virologic failure; treatment failure; lipids & glucose
<b>Statistical Methods:</b> The primary sample of subjects was the intention-to-treat sample, i.e. all subjects who had at least one dose of study medication. Data for subjects who switched to Nevirapine and missing data were dealt with in three ways for analyses of virologic failure: Switch/missing=failure: subjects who discontinued or switched treatment were included as failures beyond the last dose of original medication for the calculation of proportions. Subjects with missing data were considered failures. This was the main analysis of proportions. Switch included: subjects who switched treatment were included in the analysis irrespective of treatment outcome. Subjects with missing data were considered failures. As-treated: data from subjects who switched were not included in this analysis past the last date of original study medication. No imputations for missing data were included. For continuous data, calculations were performed on the observed data and no account was taken of whether or not subjects switched treatment. For the primary endpoint, the percentage of subjects with HIV-1 RNA <50 copies/mL was presented together with exact 95% confidence intervals. This was the same for the secondary endpoint with plasma HIV-1 RNA concentration below 3 copies/mL at each timepoint. Plasma HIV-1 RNA <50 copies/mL over time was also summarised in the same way. In addition, this endpoint was log <sub>10</sub> -transformed and summarised as continuous data. Changes from baseline were also summarised. Time to obtain an HIV-1 RNA of <50 copies/mL was analysed using Kaplan-Meier estimates. HIV-1 RNA at Weeks 24 & 48 were categorised by baseline values and summarised. CD4+ cell count & change from baseline were summarised. The adherence scores were summarised for those who were failures at Week 48. In addition, total percentage adherence was categorised and success/failure were summarised within these categories. Treatment failure was summarised as for the primary endpoint. Hodges-Lehmann methodology was used to provide point estimates and 95% confidence intervals for the changes from baseline in lipids & glucose.
<b>Study Population:</b> ART naïve subjects ≥18 years of age with a CD4+ count <200mm <sup>3</sup> , who had documented HIV-1 infection (Western blot or plasma HIV-1 RNA). Women of childbearing potential had to have a negative serum pregnancy test. Key exclusion criteria included: a known primary HIV infection; a known ongoing acute opportunistic infection; Pregnant women or women who were breast-feeding; Subjects with known current alcohol or illicit drug use or who were unlikely to refrain from drug and/or alcohol use during the study; a known history of clinically relevant pancreatitis or hepatitis in previous 6 months; known treatment with radiation therapy or cytotoxic chemotherapeutic agents in previous 30 days or an anticipated need for such treatment during the study; Treatment with immunomodulating agents in previous 30 days; Grade 3 or 4 serum aminotransferase levels in previous 30 days.

		<b>All Subjects</b>		
Number of Subjects:				
Planned, N		50		
Randomised, N		55		
Completed, n (%)		36 (65)		
Total Number Subjects Withdrawn, N (%)		19 (35)		
Withdrawn due to Adverse Events n (%)		8 (15)		
Withdrawn due to Lack of Efficacy n (%)		0		
Withdrawn for other reasons n (%)		11 (20)		
<b>Demographics</b>		<b>All Subjects</b>		
N (ITT)		55		
Females: Males		17 : 38		
Mean Age, years (SD)		36.9 (8.1)		
Black, n (%)		31 (56%)		
<b>Primary Efficacy Results: Percentage of subjects with plasma HIV-1 RNA concentration &lt;50 copies/mL at Weeks 24 &amp; 48</b>				
		<b>Switch/missing = failure</b>	<b>Switch included</b>	<b>As-treated</b>
Week 24	success (<50 copies/mL) n (%)	28 (50.9)	29 (52.7)	28 (68.3)
	failure n (%)	27 (49.1)	26 (47.3)	13 (31.7)
	95% confidence interval of success	37.1 to 64.6	38.8 to 66.3	51.9 to 81.9
Week 48	success (<50 copies/mL) n (%)	29 (52.7)	29 (52.7)	29 (82.9)
	failure n (%)	26 (47.3)	26 (47.3)	6 (17.1)
	95% confidence interval of success	38.8 to 66.3	38.8 to 66.3	66.4 to 93.4
<b>Secondary Outcome Variable(s):</b>				
		<b>Switch/missing = failure</b>	<b>Switch included</b>	<b>As-treated</b>
<b>Percentage of subjects achieving plasma HIV-1 RNA concentration below 3 copies/mL</b>				
Baseline	success (<3 copies/mL) n (%)	0	0	0
	failure n (%)	55 (100.0)	55 (100.0)	55 (100.0)
	95% confidence interval of success	0.0 to 6.5	0.0 to 6.5	0.0 to 6.5
Week 24	success (<3 copies/mL) n (%)	2 (3.6)	2 (3.6)	2 (4.9)
	failure n (%)	53 (96.4)	53 (96.4)	39 (95.1)
	95% confidence interval of success	0.4 to 12.5	0.4 to 12.5	0.6 to 16.5
Week 32	success (<3 copies/mL) n (%)	7 (12.7%)	7 (12.7%)	7 (17.9%)
	failure n (%)	48 (87.3%)	48 (87.3%)	32 (82.1%)
	95% confidence interval of success	5.3% to 24.5%	5.3% to 24.5%	7.5% to 33.5%
Week 40	success (<3 copies/mL) n (%)	6 (10.9%)	6 (10.9%)	6 (17.6%)
	failure n (%)	49 (89.1%)	49 (89.1%)	28 (82.4%)
	95% confidence interval of success	4.1% to 22.2%	4.1% to 22.2%	6.8% to 34.5%
Week 48	success (<3 copies/mL) n (%)	9 (16.4)	9 (16.4)	9 (25.7)
	failure n (%)	46 (83.6)	46 (83.6)	26 (74.3)
	95% confidence interval of success	7.8 to 28.8	7.8 to 28.8	12.5 to 43.3
<b>Percentage of subjects with plasma HIV-1 RNA &lt;50 copies/mL over time</b>				

Baseline	success (<50 copies/mL) n (%)	0	0	0
	failure n (%)	55 (100.0)	55 (100.0)	55 (100.0)
	95% confidence interval of success	0.0 to 6.5	0.0 to 6.5	0.0 to 6.5
Week 16	success (<50 copies/mL) n (%)	25 (45.5)	25 (45.5)	25 (61.0)
	failure n (%)	30 (54.5)	30 (54.5)	16 (39.0)
	95% confidence interval of success	32.0 to 59.4	32.0 to 59.4	44.5 to 75.8
Week 32	success (<50 copies/mL) n (%)	36 (65.5)	37 (67.3)	36 (92.3)
	failure n (%)	19 (34.5)	18 (32.7)	3 (7.7)
	95% confidence interval of success	51.4 to 77.8	53.3 to 79.3	79.1 to 98.4
Week 40	success (<50 copies/mL) n (%)	29 (52.7)	30 (54.5)	29 (85.3)
	failure n (%)	26 (47.3)	25 (45.5)	5 (14.7)
	95% confidence interval of success	38.8 to 66.3	40.6 to 68.0	68.9 to 95.0
<b>All Subjects (n=55)</b>				
<b>Log<sub>10</sub> HIV-1 RNA over time median (q1 to q3)</b>				
Baseline		5.45 (5.13 to 5.80)		
Week 4		3.03 (2.61 to 3.39)		
	Change from baseline at Week 4	-2.51 (-2.99 to -2.10)		
Week 8		2.23 (1.94 to 2.80)		
	Change from baseline at Week 8	-3.03 (-3.68 to -2.61)		
Week 16		2.23 (1.94 to 2.80)		
	Change from baseline at Week 16	-3.51 (-3.79 to -3.11)		
Week 24		1.45 (1.20 to 1.74)		
	Change from baseline at Week 24	-4.00 (-4.50 to -3.42)		
Week 32		1.16 (0.87 to 1.67)		
	Change from baseline at Week 32	-4.13 (-4.56 to -3.91)		
Week 40		0.95 (0.60 to 1.51)		
	Change from baseline at Week 40	-4.28 (-5.01 to -3.96)		
Week 48		1.08 (0.30 to 1.62)		
	Change from baseline at Week 48	-4.24 (-4.77 to -3.97)		
		<b>Switch/missing = failure</b>	<b>Switch included</b>	<b>As-treated</b>
<b>Time to obtain a viral load HIV-1 RNA &lt;50 copies/mL</b>				
	Median (days)	182	174	168
	25 <sup>th</sup> percentile to 75 <sup>th</sup> percentile (days)	117 to NA	114 to NA	117 to 227
<b>HIV-1 RNA &lt;50 copies/mL by baseline HIV-1 RNA (copies/mL)</b>				
Week 24	baseline: ≤100000 (n=10)			
	success (<50 copies/mL) n (%)	8 (80)	8 (80)	8 (89)
	failure n (%)	2 (20)	2 (20)	1 (11)
	baseline: >100000 to ≤500000 (n=27)			
	success (<50 copies/mL) n (%)	16 (59)	16 (59)	16 (73)
	failure n (%)	11 (41)	11 (41)	6 (27)
	baseline: >500000 (n=18)			
	success (<50 copies/mL) n (%)	4 (22)	5 (28)	4 (40)
	failure n (%)	14 (78)	13 (72)	6 (60)

Week 48			
baseline: ≤100000 (n=10)			
success (<50 copies/mL) n (%)	4 (40)	4 (40)	4 (67)
failure n (%)	6 (60)	6 (60)	2 (33)
baseline: >100000 to ≤500000 (n=27)			
success (<50 copies/mL) n (%)	18 (67)	18 (67)	18 (86)
failure n (%)	9 (33)	9 (33)	3 (14)
baseline: >500000 (n=18)			
success (<50 copies/mL) n (%)	7 (39)	7 (39)	7 (88)
failure n (%)	11 (61)	11 (61)	1 (13)
<b>HIV-1 RNA &lt;3 copies/mL by baseline HIV-1 RNA</b>			
Week 24			
baseline: ≤100000 (n=10)			
success (<3 copies/mL) n (%)	0	0	0
failure n (%)	10 (100)	10 (100)	9 (100)
baseline: >100000 to ≤500000 (n=27)			
success (<3 copies/mL) n (%)	2 (7)	2 (7)	2 (9)
failure n (%)	25 (93)	25 (93)	20 (91)
baseline: >500000 (n=18)			
success (<3 copies/mL) n (%)	0	0	0
failure n (%)	18 (100)	18 (100)	10 (100)
Week 48			
baseline: ≤100000 (n=10)			
success (<3 copies/mL) n (%)	3 (30)	3 (30)	3 (50)
failure n (%)	7 (70)	7 (70)	3 (50)
baseline: >100000 to ≤500000 (n=27)			
success (<3 copies/mL) n (%)	5 (19)	5 (19)	5 (24)
failure n (%)	22 (81)	22 (81)	16 (76)
baseline: >500000 (n=18)			
success (<3 copies/mL) n (%)	1 (6)	1 (6)	1 (13)
failure n (%)	17 (94)	17 (94)	7 (88)
	<b>All Subjects (n=55)</b>		
<b>Change in CD4+ cell count (cells/mm<sup>3</sup>)</b>			
Median (q1 to q3)			
Baseline	54 (23 to 98)		
Week 4	137 (82 to 191)		
change from baseline at 4 weeks	72 (21 to 111)		
Week 8	166 (108 to 231)		
change from baseline at 8 weeks	107 (43 to 145)		
Week 16	186 (116 to 256)		
change from baseline at 16 weeks	98 (39 to 164)		
Week 24	178 (137 to 288)		
change from baseline at 24 weeks	116 (62 to 217)		
Week 32	233 (148 to 314)		
change from baseline at 32 weeks	174 (67 to 272)		
Week 40	241 (155 to 365)		
change from baseline at 40 weeks	148 (80 to 266)		
Week 48	256 (180 to 358)		
change from baseline at 48 weeks	190 (115 to 282)		
	<b>Trizivir</b>	<b>Efavirenz</b>	<b>Total</b>
<b>Adherence and correlation with the virologic failure</b>			
% adherence scores for subjects failing to achieve HIV-RNA <50 copies/mL at Week 48			
Switch/missing = failure: median (q1 to q3) (n=26)			
Week 4	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)
Week 24	100 (93 to 100)	100 (100 to 100)	100 (95 to 100)
Week 48	100 (96 to 100)	100 (100 to 100)	100 (98 to 100)

Switch included: median (q1 to q3) (n=26)			
Week 4	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)
Week 24	100 (93 to 100)	100 (100 to 100)	100 (95 to 100)
Week 48	100 (96 to 100)	100 (100 to 100)	100 (98 to 100)
As-treated: median (q1 to q3) (n=6)			
Week 4	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)
Week 24	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)
Week 48	100 (93 to 100)	100 (100 to 100)	100 (95 to 100)
	<b>Switch/missing = failure</b>	<b>Switch included</b>	<b>As-treated</b>
<b>Categorised total adherence scores (success: &lt;50 copies/mL at Week 48)</b>			
Week 4			
Total score <95% success n (%)	3 (100)	3 (100)	3 (100)
failure n (%)	0	0	0
Total score ≥95% success n (%)	22 (52)	22 (52)	22 (81)
failure n (%)	20 (48)	20 (48)	5 (19)
Week 24			
Total score <95% success n (%)	3 (50)	3 (50)	3 (100)
failure n (%)	3 (50)	3 (50)	0
Total score ≥95% success n (%)	19 (66)	19 (66)	19 (79)
failure n (%)	10 (34)	10 (34)	5 (21)
Week 48			
Total score <95% success n (%)	1 (50)	1 (50)	1 (50)
failure n (%)	1 (50)	1 (50)	1 (50)
Total score ≥95% success n (%)	21 (75)	21 (75)	21 (81)
failure n (%)	7 (25)	7 (25)	5 (19)
<b>Treatment failure</b>			
Treatment failure n (%)	32 (58.2)	32 (58.2)	31 (56.4)
Not treatment failure n (%)	23 (41.8)	23 (41.8)	24 (43.6)
95% confidence interval for % of treatment failures	44.1 to 71.4	44.1 to 71.4	42.3 to 69.7
<b>Lipids</b>			
	<b>All Subjects (n=55)</b>		
<b>Total cholesterol (mmol/L) Median (q1 to q3)</b>			
Baseline	3.87 (3.34 to 4.56)		
Week 24	4.92 (4.50 to 5.47)		
change from baseline at Week 24	0.91 (0.26 to 1.74)		
Week 48	5.04 (4.42 to 6.19)		
change from baseline at Week 48	0.89 (0.35 to 1.97)		
<b>LDL cholesterol (mmol/L) Median (q1 to q3)</b>			
Baseline	2.19 (1.70 to 2.95)		
Week 24	2.96 (2.51 to 3.29)		
change from baseline at Week 24	0.41 (-0.02 to 1.09)		
Week 48	3.05 (2.42 to 4.00)		
change from baseline at Week 48	0.52 (0.03 to 1.43)		
<b>HDL cholesterol (mmol/L) Median (q1 to q3)</b>			
Baseline	0.92 (0.71 to 1.09)		
Week 24	1.33 (1.13 to 1.69)		
change from baseline at Week 24	0.39 (0.23 to 0.54)		
Week 48	1.27 (1.15 to 1.70)		
change from baseline at Week 48	0.46 (0.21 to 0.65)		
<b>Total triglycerides (mmol/L) Median (q1 to q3)</b>			
Baseline	1.28 (0.90 to 2.18)		
Week 24	1.22 (0.91 to 1.68)		
change from baseline at Week 24	0.13 (-0.34 to 0.32)		

Week 48 change from baseline at Week 48	1.36 (0.91 to 2.17) 0.15 (-0.29 to 0.69)
<b>Glucose (mmol/L) Median (q1 to q3)</b>	
Baseline	4.80 (4.50 to 5.40)
Week 24 change from baseline at Week 24	5.20 (4.90 to 5.60) 0.35 (-0.20 to 0.90)
Week 48 change from baseline at Week 48	5.10 (4.65 to 5.40) 0.40 (-0.25 to 0.70)
<b>Safety Results:</b> An on-therapy adverse event (AE) – serious and non-serious – was defined as an AE with onset on or after the first day of study medication but no later than the last day of study medication.	
	<b>All Subjects (n=55)</b>
<b>Most Frequent Adverse Events – On-Therapy</b>	<b>n (%)</b>
Subjects with any AE(s), n(%)	53 (96)
Nausea	21 (38)
Dreams	14 (25)
Headache	11 (20)
Common cold	11 (20)
Dizziness	11 (20)
Vomiting	10 (18)
Insomnia	10 (18)
Rash	8 (15)
Diarrhoea	8 (15)
Decreased appetite	7 (13)
<b>Serious Adverse Events - On-Therapy</b>	
<b>n (%) [n considered by the investigator to be related to study medication]</b>	
	<b>All Subjects</b>
Subjects with non-fatal SAEs, n (%)	9 (16)
	<b>n (%) [related]</b>
Primary brain lymphoma	1 (2) [0]
Cerebral infarction	1 (2) [0]
Pulmonary embolism	1 (2) [0]
Adverse effect of abacavir	1 (2) [1]
Abnormal liver function test(s)	1 (2) [1]
Pneumonia	1 (2) [0]
Grand mal epileptic convulsion(s)	1 (2) [0]
Allergy to abacavir	2 (4) [2]
Allergy to efavirenz	1 (2) [1]
Allergy to shellfish	1 (2) [0]
Cellulites of foot	1 (2) [0]
Subjects with fatal SAEs, n (%)	0

**Conclusion:**

See publications below.

**Publications:**

Wilkins E, Gazzard B, Easterbrook P et al., Efficacy of Quad Therapy in Antiretroviral Naïve Adults with Very Low CD4 Cell Counts: The TETRA Study. 6th International Congress on Drug Therapy in HIV Infection, 2002, Poster P13

Easterbrook P, Wilkins E, Gazzard B, et al., Efficacy and Tolerability of Trizivir plus Efavirenz in Antiretroviral Naïve Adults with Advanced HIV Disease at 48 Weeks: The TETRA Study. Poster 4745, ICAAC 2003, Poster P4745

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