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<b>Study No.:</b> AZL30002 TRIZAL
<b>Title:</b> A Phase IIIb, Randomised, Open-Label, Multicentre Study to Evaluate the Safety and Efficacy of a Triple Combination Tablet (Trizivir) [abacavir, lamivudine, zidovudine] Versus Continued Antiretroviral Triple Therapy in HIV-1 Infected Subjects with Undetectable Plasma HIV-1 RNA Levels (TRIZAL)
<b>Rationale:</b> HIV disease progression, including opportunistic infections and mortality, can be profoundly altered by Highly Active Antiretroviral Therapy (HAART). During HAART, suppressing plasma HIV-1 RNA to undetectable levels greatly limits the selection of drug resistant virus associated with treatment failure, and is one of the main goals of treatment intervention. However, a number of factors may confound a regimen's ability to achieve virological suppression, these include but are not limited to, poor tolerability, interactions with concomitant medications, and inadequate long-term adherence due to complex daily regimens. In addition to the complexities of managing virological suppression, both clinical and metabolic toxicities such as elevated triglyceride and cholesterol levels have prompted physicians to reconsider the risks and benefits of these agents, particularly in early disease. Compact HAART regimens are needed to improve the management of HIV infection. Such regimens may facilitate patient compliance and may enhance therapeutic success by limiting the emergence of resistant virus due to suboptimal viral suppression. The combination of abacavir/lamivudine/zidovudine (ABC/3TC/ZDV triple combination tablet) has many of the desirable characteristics of a compact regimen. The combination may be effective in suppressing viral replication, all the components have simple dosing schedules without restrictive dietary requirements and there is low potential for drug-drug interactions with other therapies for HIV and opportunistic infections.
<b>Phase:</b> 3b
<b>Study Period:</b> 15-Nov-1999 to 22-Mar-2001
<b>Study design:</b> This Phase IIIb, 48 week, randomised, open-label, parallel group, international multicentre study, was designed to compare the antiviral effect and durability of response (as measured by plasma HIV-1 RNA) and safety of ABC/3TC/ZDV triple combination tablet compared with continued therapy with a triple combination antiretroviral regimen containing 3 NRTIs, or 2 NRTI+ 1 NNRTI or 2 NRTIs + 1 PI.
<b>Centres .:</b> 47 European centres : Belgium (2), France (22), Germany (6),Ireland (1), Italy (4), Portugal (2), Spain(1), Sweden (2) and United Kingdom (7)
<b>Indication:</b> HIV-1 infected subjects, pretreated
<b>Treatment:</b> Study drug was defined as ABC/3TC/ZDV triple combination tablet only. ABC/3TC/ZDV triple combination tablet was supplied as 300/150/300mg of abacavir/lamivudine/zidovudine combination tablet. Reference therapy: Reference study drugs were defined as continued open label ART taken as prescribed prior to baseline.
<b>Objectives:</b> Primary Objective To compare treatment failure with ABC/3TC/ZDV triple combination tablet versus continued combination antiretroviral therapy with 3 NRTIs or 2 NRTIs and a NNRTI or 2 NRTIs and a PI, in subjects with undetectable viral load (< 50 HIV-1 RNA copies/mL). Secondary Objectives To evaluate the immunological response to ABC/3TC/ZDV triple combination tablet versus a continued combination antiretroviral regimen of 3 NRTIs or 2 NRTIs and a NNRTI or 2 NRTIs and a PI. To assess the safety and tolerance of ABC/3TC/ZDV triple combination tablet versus a continued combination antiretroviral regimen of 3 NRTIs or 2 NRTIs and a NNRTI or 2 NRTIs and a PI. To assess the adherence to and satisfaction with ABC/3TC/ZDV triple combination tablet versus a continued combination antiretroviral regimen of 3 NRTIs or 2 NRTIs and a NNRTI or 2 NRTIs and a PI.
<b>Primary Outcome/Efficacy Variable:</b> Treatment failure was defined as a virological failure (two consecutive HIV-1 RNA values $\geq$ 400 copies/ml) or a switch from randomised therapy or premature discontinuation.
<b>Secondary Outcome/Efficacy Variable(s):</b> The efficacy parameters were changes in plasma HIV-1 RNA and lymphocyte counts and disease progression.
<b>Statistical methods:</b> The primary Population for the primary efficacy analyses was the Intent-to-Treat (ITT, S=F) population. The ITT, S=F Population was defined as all subjects who were randomised and received at least one dose of the study drug. Subjects in the continued ART group were included if they continued the study after Day 1. Subjects who were randomised but did not initiate therapy were excluded. The S=F, switch=failure, meant that a subject's

response was considered as a "failure" if any of the following criteria were met :  
 The subject experienced a virological failure (two consecutive HIV-1 RNA values  $\geq$  400 copies/mL), or the subject prematurely discontinued randomised therapy for any reason (ie, dropped out of the study, changed any component of the randomised treatment regimen).

**As Treated population**

This population corresponds to the Per protocol population, in which only data collected for subjects while on randomised therapy contribute to the analysis. Subjects discontinuing, taking prohibited medication or switching antiretroviral treatment were excluded in this analysis population beyond the last dose of originally randomised drug. Additionally, major protocol violators were excluded. No imputations for missing data were performed for this population.

**Safety population**

This population was defined as all subjects who initiated study drug treatment (received at least one dose of study drug).

**Study Population:**

The main eligibility criterion was plasma HIV-1 RNA PCR < 50 copies/mL at screening with a history of plasma HIV-1 RNA undetectability (< 400 copies/mL) for at least 6 months on the subjects first antiretroviral combination regimen of one of the following combinations of treatment: 3 NRTI's or 2 NRTI's + 1 PI or 2NRTI's + 1 NNRTI.

	Treatment Groups		
	ABC/3TC/ZDV triple combination tablet	Continued ART	Total
<b>No. Randomised</b>	<b>111</b>	<b>108</b>	<b>219</b>
No. Treated	106	103	209
No. Never Initiated Treatment	5	5	10
<b>No. (%) Completed 48 Weeks on Study</b>	<b>97 (92)<sup>a</sup></b>	<b>100 (97)<sup>a</sup></b>	<b>197 (94)<sup>a</sup></b>
Completed study on randomised treatment	<b>85 (80)<sup>a</sup></b>	<b>81 (79)<sup>a</sup></b>	<b>166 (79)<sup>a</sup></b>
Completed study on non-randomised treatment	12 (11)	19 (18)	31 (15)
<b>No. (%) Discontinued Study Prior to Week 48</b>	<b>9 (8)<sup>a</sup></b>	<b>3 (3)<sup>a</sup></b>	<b>12 (6)<sup>a</sup></b>
Withdrawn due to Adverse Events, n(%)	4 (4)	0	4 (2)
Withdrawn due to Lack of Efficacy, n(%)	0	0	0
Withdrawn for Other Reasons, n(%)	5 (4)	3(3)	8 (4)
<b>No. (%) Discontinued Randomised Treatment Prior to Week 48</b>	<b>21 (20)</b>	<b>22 (21)</b>	<b>43 (21)</b>
Primary Reason for Discontinuing Randomised Treatment Prior to Week 48			
Withdrawn due to Lack of Efficacy, n(%)	1 (<1)	0	1 (<1)
Withdrawn for Other Reasons, n(%)	4(4)	6(6)	10(5)
Percentages based on number of treated subjects.			

Demographics			
	Treatment Groups		
	ABC/3TC/ZDV triple combination tablet N=106 n (%)	Continued ART N=103 n (%)	Total N=209 n (%)
CDC Classification (n, %):			
Asymptomatic (Class A)	70 (66)	76 (74)	146 (70)
Symptomatic, not AIDS (Class B)	15 (14)	12 (12)	27 (13)
AIDS (Class C)	21 (20)	15 (15)	36 (17)

Proportions <50 copies/mL <sup>a</sup>			
2NRTIs + PI	61 (92)	62 (95)	123 (94)
2NRTIs + nNRTI	19 (95)	16 (80)	35 (88)
3NRTIs	17 (94)	15 (83)	32 (89)
Others	1	0	1
<b>Total Study Population</b>	<b>98 (92)</b>	<b>93 (90)</b>	<b>191 (91)</b>
Median CD4+ cell count (cells/mm <sup>3</sup> )	487 (N=66)		
2NRTIs + PI	481 (N=19*)	534 (N=65)	505 (N=131)
2NRTIs + nNRTI	506 (N=18)	466 (N=20)	481 (N=39)
3NRTIs	(291,626) (N=2)	403 (N=18)	467 (N=36)
Others (individual values)	<b>482 (N=105)</b>	0	(291,626) (N=2)
<b>Total Study Population</b> (min, max)	(134, 1246)	<b>504 (N=103)</b>	<b>494 (N=208)</b>
Split by strata (cells/mm <sup>3</sup> ):		(133, 1324)	(133, 1324)
100-300	23 (22)		
300-500	31 (30)	19 (18)	42 (20)
≥500	51 (49)	32 (31)	63 (30)
		52 (50)	103 (50)
As measured by the ROCHE AMPLICOR HIV-1 MONITOR test (Primers v1.5, Ultrasensitive, LOD=50 copies/mL). *One missing value			
<b>Primary Efficacy Results: Treatment failure over 48 weeks (ITT, S =F)</b>			
	<b>Treatment Groups</b>		
	ABC/3TC/ZDV triple combination tablet <b>N=106</b>	<b>Continued ART N=103</b>	<b>Total N=209</b>
Total Population			
Virological failure <sup>a</sup>	5 (5)	1 (<1)	6 (3)
Failure due to switch <sup>b</sup>	18 (17)	22 (21)	40 (19)
Total	23 (21.7)	23 (22.3)	46 (22)
Difference in proportions of treatment failures	0.63%	Unstratified 90% CI (-8.8, 10.1)	
		Unstratified 95% CI (-10.6, 11.9)	
Stratified by Prior ART			
2NRTIs+PI	16/66 (24)	16/65 (25)	32/131 (24)
2NRTIs+NNRTI	4/20 (20)	5/20 (25)	9/40 (23)
3NRTIs	2/18 (11)	2/18 (11)	4/36 (11)
Other	1/2 (50)	0	1/2 (50)
<b>Difference in proportions of treatment failures</b>	<b>1.20</b>	<b>Stratified 90% CI (-8.3, 10.7)</b>	
		Stratified 95% CI (-10.1, 12.5)	
a Defined as two consecutive plasma HIV-1RNA ≥400 copies/mL. b Change to randomised medication or permanent discontinuation			
<b>Secondary Outcome Variable(s):</b>			
Plasma HIV RNA at 48 weeks	ABC/3TC/ZDV triple combination tablet	<b>Continued ART</b>	
ITT ≤50 copies/mL at week 48, %	75	69	
As Treated ≤50 copies/mL at week 48, %	94	90	
95% confidence interval	Not available (na)	na	
Median CD4+ Cell Count Changes from Baseline	ABC/3TC/ZDV triple combination tablet Cells/mm <sup>3</sup> (n)	<b>Continued ART</b> Cells/mm <sup>3</sup> (n)	
Treatment week –ITT			
Median Baseline	482(106)	504(103)	
Week 4	32(101)	7(98)	

Week 8	20(94)	28(101)
Week 16	50(96)	40(101)
Week 24	65(97)	39(99)
Week 36	39(93)	25(94)
Week 48	26(90)	26(96)
Median CD8+ Cell Count Changes from Baseline	ABC/3TC/ZDV triple combination tablet Cells/mm <sup>3</sup> (n)	<b>Continued ART</b> Cells/mm <sup>3</sup> (n)
Treatment week -ITT		
Median Baseline	778(105)	811(109)
Week 4	38(101)	-13(98)
Week 8	34(94)	29(101)
Week 16	53(96)	1(101)
Week 24	22(97)	13(99)
Week 36	26(93)	-56(94)
Week 48	-11(90)	-69(96)

<b>Most Frequent Adverse Events – On-Therapy</b>		
<b>Adverse Events Reported by ≥ 10% of Subjects in Either Treatment Group</b>		
	ABC/3TC/ZDV triple combination tablet	Continued ART
	<b>N=106</b>	<b>N=103</b>
<b>Adverse Event</b>	<b>n (%)</b>	<b>n (%)</b>
Any Adverse Event	83 (78%)	80 (78%)
Malaise and fatigue	20 (19%)	12 (12%)
Diarrhoea	14 (13%)	13 (13%)
Allergies and Allergic Reactions <sup>a</sup>	11 (10%)	0
Weight problems <sup>b</sup>	9 (8%)	13 (13%)
Significantly different This group term includes the following verbatim texts : abdominal fat change(s); abdominal fat charge ; abdominal fat wasting ; arm(s) fat wasting ; buttock(s) fat loss ; facial wasting ; fat loss on buttocks ; fat loss on legs ; increased abdominal fat ; leg(s) fat wasting ; loss of weight ; slight weight loss ; weight loss.		

<b>Adverse Events Considered Possibly Related to Study Medication &gt;5% of Subjects in Either Treatment Group</b>		
	ABC/3TC/ZDV triple combination tablet	Continued ART
	<b>N=106</b>	<b>N=103</b>
<b>Adverse Event</b>	<b>n (%)</b>	<b>n (%)</b>
Any Adverse Event	37 (35)	30 (29)
Malaise and fatigue	11 (10)	3 (3)
Allergies and Allergic Reactions	11 (10)	0
Weight problems <sup>a</sup>	4 (4)	9 (9)
Diarrhoea	5 (5)	7 (7)
Nausea and vomiting	6 (6)	4 (4)
A This group term includes the following verbatim texts : abdominal fat change(s); abdominal fat charge ; abdominal fat wasting ; arm(s) fat wasting ; buttock(s) fat loss ; facial wasting ; fat loss on buttocks ; fat loss on legs ; increased abdominal fat ; leg(s) fat wasting ; loss of weight ; slight weight loss ; weight loss.		
<b>Serious Adverse Events per Body System</b>		
Serious Adverse Event	<b>ABC/3TC/ZDV triple combination tablet N=106</b>	<b>Continued ART N=103</b>
Any Serious Adverse Event	17(16)	5(5)
Non-site specific <sup>a</sup>	12(12)	0
Drug interaction overdose and trauma	1(<1)	1(<1)
Lower respiratory	1(<1)	1(<1)
Blood & lymphatic	0	1(<1)
Cardiovascular	1(<1)	0
Gastrointestinal	1(<1)	0
Hepatobiliary tract & pancreas	1(<1)	0
Pregnancy <sup>b</sup>	0	1(<1)
Reproduction	1(<1)	0
Urology	0	1(<1)
Subjects with Fatal SAEs, n (%)	0	0

<sup>a</sup> Allergies and allergic reactions, temperature regulation disturbances

<sup>b</sup> Abortion and stillbirth

**Conclusion:**

See publications below.

**Publications :**

C Katlama, S Fenske, B Gazzard, A Lazzarin, N Clumeck, J Mallolas, A Lafeuillade, J-P Mamet, L Beauvais TRIZAL study: switching from successful HAART to Trizivir™ (abacavir-lamivudine-zidovudine combination tablet): 48 weeks efficacy, safety and adherence results HIV Medicine 2003 4:2 p. 79

Lafeuillade A, Clumeck N, Mallolas J, Jaeger H, Livrozet JM, Ferreira Mdo S, Johnson M, Cheret A, Antoun Z; European Trizal team. Comparison of metabolic abnormalities and clinical lipodystrophy 48 weeks after switching from HAART to Trizivir versus continued HAART: the Trizal study. HIV Clin Trials. 2003 Jan-Feb;4(1):37-43

C. Katlama, N. Clumeck, S. Fenske, J. Mallolas, A. Lafeuillade, L. Beauvais. Use of Trizivir to Simplify Therapy in HAART Experienced Patients with Long Term Suppression of HIV-RNA : TRIZAL Study (AZL30002) 24 Weeks Results. Abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, USA. (Abstract / Poster Number 316)

Katlama C, Fenske S, Gazzard B, Lazzarin A, Beauvais L. Switch to Trizivir versus Continued HAART Provides Equivalent HIV-1 RNA Suppression at 48 Weeks (TRIZAL: AZL30002). In: Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, USA. Abstract Number Oral #671

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