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<b>Study No:</b> COL30494
<b>Title:</b> An Open-Label Multicentre Study to Evaluate the Adherence to, General Satisfaction and Quality of Life After 24 Weeks Therapy With a Triple Combination tablet (TRIZIVIR™) [Abacavir, Lamivudine, and Zidovudine] in HIV-1 Infected Subjects With Undetectable Plasma HIV-1 RNA Levels
<b>Rationale:</b> The combination of abacavir/lamivudine/zidovudine (ABC/LAM/ZDV)[Trizivir, TZV] triple combination tablet has many of the characteristics of a compact regimen. The combination is effective in suppressing viral replication, all the components have simple dosing requirements, without restrictive dietary requirements, and there is low potential for drug-drug interactions with other therapies for human immunodeficiency virus (HIV) and opportunistic infections. One therapeutic indication for the triple combination tablet TZV is as a simplified switch regimen for subjects with adequate virologic suppression. It would be scientifically interesting to know whether the use of TZV would benefit HIV subject adherence, and as consequence of it, have adequate HIV control for a longer time.
<b>Phase:</b> IIb-IV
<b>Study Period:</b> 02 May 2001 to 14 Mar 2002
<b>Study Design:</b> This was an open-label, multi-centre, prospective, non-randomized study. Following screening, which occurred ≤14 days before the first dosing, HIV-1 infected subjects were switched from highly active antiretroviral therapy (HAART) to TZV. Eligible subjects returned to the clinic at day 1 (first day of study drug administration) and Weeks 12 and 24. Subjects received treatment until Week 24, unless they met the protocol defined switch criterion or experienced treatment-related adverse events (AEs) (sufficiently severe for the subject to prematurely discontinue randomized treatment).
<b>Centres:</b> 36 centres in Spain
<b>Indication:</b> HIV infection
<b>Treatment:</b> Abacavir 300mg/Lamivudine 150 mg/Zidovudine 300mg [TZV] twice daily (bid) as a fixed dose combination
<b>Objectives:</b> The primary objective of the study was to assess the adherence to and general satisfaction with TZV compared with a standard antiretroviral therapy (ART) regimen containing 3 nucleoside reverse transcriptase inhibitors (NRTIs) or 2 NRTIs + 1 non-nucleoside reverse transcriptase inhibitor (NRTI) or 2 NRTIs + 1 protease inhibitor (PI), in HIV-1 subjects with undetectable viral load (<400 HIV-1 ribonucleic acid [RNA] copies/mL).
<b>Primary Outcome/Efficacy Variables:</b> The primary efficacy endpoints were as follows: Treatment Adherence (ADH) assessed by subject self report at Week 24 General Satisfaction (GS), defined as the ability to take medication, pill burden and size, timetable, food conditions and preference for regimen at baseline and Week 24
<b>Secondary Outcome/Efficacy Variables:</b> The secondary endpoint was quality of life (QOL) as measured by medical outcomes study (MOS)-HIV questionnaire at baseline and Week 24.
<b>Statistical Methods:</b> The study database was considered to be observational; no sample size calculations were required. Three populations were analysed: 1) the intent-to-treat (ITT) population consisted of subjects who received at least 1 dose of study medication (excluded major protocol violators), 2) the per- protocol (PP) population consisted of subjects who completed 24 weeks of study treatment (excluded minor protocol violators), and 3) the safety population consisted of all subjects who were examined at the baseline visit and had received at least 1 dose of study medication. Summary tabulations consisted of means, medians, standard deviations (SD), minimum, and maximum for continuous variables. For frequency variables, summary tabulations consisted of counts and percents. Summary statistics were provided for baseline or screening and each visit as well as for change-from-baseline or screening data. The primary endpoint was to evaluate ADH and GS with TZV over 24 weeks. GS was also compared to previous value with standard ART, as measured by a visual analog scale (VAS). The secondary endpoint was to assess the QOL of subjects treated with TZV over 24 weeks compared with baseline, as measured by MOS-HIV questionnaire. The VAS and MOS questionnaire were verified by Kolmogorov-Smirnov test and differences were calculated by t-test or U Mann Whitney-Wilcoxon test.
<b>Study Population:</b> Male and (non-pregnant/non-lactating) female subjects aged ≥18 years with properly documented HIV-1 infection, documented history of undetectable HIV-1 RNA values <400 copies/mL for at least 6 months prior to screening, had 1 screening HIV-1 RNA <400 copies/mL (Roche Ultra-sensitive assay) within 21 days prior to study drug administration, and were willing to reduce pill burden were eligible for study participation. In addition, subjects who had an initial treatment with 1 of the following 3 regimens for a minimum of 6 months prior to study entry were eligible for study participation: 2 NRTIs + 1 PI, 2 NRTIs + 1 NNRTI, or 3 NRTIs.

Subjects were not eligible if they were suffering from a serious medical condition that in the opinion of the investigator would compromise the safety of the subject; had creatinine level >2.0 mg/dL; had a known allergy to TZV or to any of its compounds (ZDV, LAM, or ABC); had failed to ZDV (monotherapy or bi-therapy regimens); or had hemoglobin concentration <100 g/L for men and <90 g/L for women, neutrophil count <1 (10e9/l), platelet count <50 (10e9/l), aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) >5 times the upper limit of normal (ULN), or serum pancreatic amylase and lipase >2 times the ULN within 21 days prior to the first dose of treatment.

<b>Number of Subjects:</b>	<b>Total</b>	
Screened, N	224	
Dosed (Safety Population), N	215	
ITT Population, N	195	
Completed (PP Population), n (%)	141 (66)	
Total Number Subjects Withdrawn, n (%)	74 (34)	
Withdrawn Due to AEs, n (%)	23(10)	
Withdrawn Due to Lack of Efficacy, n (%)	0	
Withdrawn For Other Reasons, n (%)	51 (24) <sup>a</sup>	
a. Of the 74 subjects withdrawn, 20 were due to major protocol violations and 31 were due to missing follow-up.		
<b>Demographics:</b>	<b>Total</b>	
N (ITT Population)	195	
Females:Males, n:n	47:148	
Mean Age in Years (SD)	41 (9)	
Caucasian, n (%)	191 (98)	
CDC Category, n (%)		
A	101 (52)	
B	33 (17)	
C	61 (31)	
Transmission, n (%)		
Homosexual	66 (34)	
Heterosexual	48 (25)	
Injection Drug Users	71 (36)	
Haemophiliacs	1 (0.5)	
Blood Transfusion	1 (0.5)	
Unknown/Others	2 (1)	
Not Applicable	6 (3)	
<b>Primary Efficacy Results (ITT and PP Populations):</b>		
<b>ADH (days) to TZV (ITT Population)</b>	<b>TZV N=195</b>	
n	192	
Mean (SD)	156 (52)	
Minimum	3	
1 <sup>st</sup> Quartile	169	
Median	179	
3 <sup>rd</sup> Quartile	180	
Maximum	199	
<b>Number of Adherent Subjects According to Different HIV-1 Transmission (ITT Population)</b>	<b>TZV</b>	
	<b>N</b>	<b>n (%)</b>
Homosexual	66	59 (89.4)
Heterosexual	48	37 (77)
Injection Drug Users	71	52 (75)
Haemophiliacs	1	1 (100)
Blood Transfusion	1	1 (100)
Others	2	2 (100)
<b>ADH (days) to TZV (PP Population)</b>	<b>TZV N=141</b>	
n	139	

Mean (SD)	177 (6.9)		
Minimum	136		
1 <sup>st</sup> Quartile	177		
Median	179		
3 <sup>rd</sup> Quartile	180		
Maximum	199		
<b>Number of Adherent Subjects According to Different HIV-1 Transmission (PP Population)</b>	<b>TZV</b>		
	<b>N</b>	<b>n (%)</b>	
Homosexual	52	51 (98)	
Heterosexual	34	33 (97)	
Injection Drug Users	46	46 (100)	
Haemophiliacs	1	1 (100)	
Blood Transfusion	1	1 (100)	
Others	2	2 (100)	
<b>GS (ITT Population)</b>	<b>TZV N=195</b>		
	<b>Baseline VAS</b>	<b>Week 24 VAS</b>	<b>Difference</b>
n	190	191	190
Mean (SD)	54.3 (28.5) <sup>a</sup>	82.3 (22.9) <sup>a</sup>	27.9 (29.7)
Minimum	1	5	-20
1 <sup>st</sup> Quartile	30	79	0
Median	55	92	20
3 <sup>rd</sup> Quartile	80	97	53
Maximum	100	100	95
GS was assessed using a 100-mm point VAS.			
a. Week 24 VAS compared with baseline VAS was statistically significant (p<0.0001).			
<b>GS According to Centre for Disease Control and Prevention (CDC HIV classification) at Week 24 (ITT Population)</b>	<b>TZV N=195</b>		
	<b>CDC Category</b>		
	<b>A</b>	<b>B</b>	<b>C</b>
n	98	32	60
Mean (SD)	26.9 (29.7)	24.2 (29.2)	31.6 (30)
Minimum	-20	-20	30
1 <sup>st</sup> Quartile	0	0	1.5
Median	24	9.5	22.5
3 <sup>rd</sup> Quartile	48	52.5	56.5
Maximum	95	80	87
<b>GS (PP Population)</b>	<b>TZV N=141</b>		
	<b>Baseline VAS</b>	<b>Week 24 VAS</b>	<b>Difference</b>
n	141	141	141
Mean (SD)	53 (28) <sup>a</sup>	90 (13) <sup>a</sup>	37 (29)
Minimum	1	5	-20
1 <sup>st</sup> Quartile	29	87	12
Median	54	95	30
3 <sup>rd</sup> Quartile	77	98	62
Maximum	100	100	95
GS was assessed using a 100-mm point VAS.			
a. Week 24 VAS compared with baseline VAS was statistically significant (p<0.0001).			
<b>GS According to CDC Classification at Week 24 (PP Population)</b>	<b>TZV N=141</b>		
	<b>CDC Category</b>		
	<b>A</b>	<b>B</b>	<b>C</b>
n	69	24	48
Mean (SD)	37 (29)	32 (30)	39 (29)

Minimum	-20	-20	-19
1 <sup>st</sup> Quartile	16	6	14
Median	27	27	44
3 <sup>rd</sup> Quartile	61	60	64
Maximum	95	80	87
<b>Secondary Efficacy Results (ITT and PP Populations):</b>			
<b>Change From Baseline in QOL (ITT Population)</b>	<b>TZV N=195</b>		
	<b>Baseline</b>	<b>Week 24</b>	<b>Difference</b>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
n	193	193	193
General Health	58 (25)	67 (32)	1 (20)
Pain	84 (22)	83 (22)	-2 (18)
Physical Health	87 (18)	87 (18)	-1 (13)
Role Functioning	90 (26)	89 (27)	-1 (25)
Social Functioning	88 (22)	89 (21)	1 (16)
Mental Health	70 (21)	70 (20)	1 (14)
Energy	69 (23)	68 (23)	-1 (19)
Health Problems	82 (22)	83 (21)	2 (17)
Cognitive Function	80 (20)	81 (21)	1 (16)
Overall QOL	67 (20)	70 (20)	3 (20)
Transient Health	63 (20)	66 (21)	3 (24)
<b>Change From Baseline in QOL According to CDC Classification at Week 24 (ITT Population)</b>	<b>TZV N=195</b>		
	<b>A</b>	<b>B</b>	<b>C</b>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
n	193	193	193
General Health	2 (22)	-1 (22)	1 (16)
Pain	-1 (17)	-6 (15)	-1 (22)
Physical Health	0 (9)	0 (12)	-2 (18)
Role Functioning	1 (22)	3 (21)	-7 (32)
Social Functioning	2 (15)	-1 (11)	1 (18)
Mental Health	1 (14)	-0 (15)	0 (13)
Energy	-2 (17)	-1 (17)	1 (22)
Health Problems	3 (15)	2 (15)	0 (21)
Cognitive Function	1 (13)	3 (20)	-1 (19)
Overall QOL	5 (21)	6 (15)	0 (19)
Transient Health	4 (22)	7 (26)	1 (26)
<b>Change From Baseline in QOL (PP Population)</b>	<b>TZV N=141</b>		
	<b>Baseline</b>	<b>Week 24</b>	<b>Difference</b>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
n	138	138	138
General Health	58 (26)	62 (27)	1 (24)
Pain	85 (22)	85 (20)	-3 (22)
Physical Health	88 (19)	88 (17)	-1 (15)
Role Functioning	91 (25)	90 (27)	-2 (29)
Social Functioning	89 (22)	91 (19)	1 (19)
Mental Health	71 (21)	72 (20)	1 (16)
Energy	70 (23)	70 (22)	-1 (22)
Health Problems	82 (22)	85 (19)	3 (20)
Cognitive Function	81 (20)	84 (19)	2 (19)
Overall QOL	68 (21)	73 (20)	4 (23)
Transient Health	62 (21)	67 (21)	4 (28)

Change From Baseline in QOL According to CDC Classification at Week 24 (PP Population)	TZV N=141		
	A	B	C
	Mean (SD)	Mean (SD)	Mean (SD)
n	138	138	138
General Health	2 (27)	-1 (26)	1 (18)
Pain	-2 (21)	-9 (18)	-1 (25)
Physical Health	- 1 (11)	-1 (14)	-2 (21)
Role Functioning	1 (24)	4 (26)	-8 (35)
Social Functioning	2 (18)	- 2 (13)	2 (22)
Mental Health	1 (17)	-1 (18)	1 (16)
Energy	-3 (21)	-1 (20)	1 (25)
Health Problems	4 (17)	3 (17)	0 (24)
Cognitive Function	3 (16)	5 (24)	- 1 (21)
Overall QOL	4 (16)	5 (24)	- 1 (22)
Transient Health	4 (25)	9 (30)	- 1 (29)
<b>Safety Results:</b> All AEs were collected from screening through the follow-up period.			
Most Frequent Adverse Events – On Therapy	TZV N=215		
Subjects With Any AEs, n (%)	90 (42)		
Total Number of AEs	148		
General Symptoms, n (%)	69 (46)		
Respiratory Disorders, n (%)	14 (9)		
Central And Peripheral Nervous System Disorders, n (%)	14 (9)		
Urine System Disorders, n (%)	5 (3)		
Gastrointestinal Disorders, n (%)	13 (9)		
Immunological Disorders (Increased Viral Load)	10 (7)		
Skin Disorders, n (%)	5 (4)		
Metabolic And Nutritional Disorders, n (%)	4 (3)		
Musculoskeletal Disorders, n (%)	4 (3)		
Haematological Abnormalities, n (%)	2 (1)		
Bacterial And Viral Infections, n (%)	4 (3)		
Non-Site Specific, n (%)	4 (3)		
*Percentage of AE per group have been calculated based on total number of AE and not subjects with AE			
Serious Adverse Events – On Therapy n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]	TZV N=215 n (%) [related]		
Subjects With Non-Fatal SAEs	26 (12) [20]		
Pancytopenia	1(0.5) [1]		
Hepatitis	1(0.5)[0]		
Abacavir Hypersensitivity Reaction	19 (9) [19]		
Depression	1(0.5) [1]		
Haemoptysis	1 (0.5) [1]		
Respiratory infection	1(0.5) [1]		
Traumatisms	1(0.5) [1]		
Pneumonia	1(0.5) [1]		
Appendicitis	1(0.5) [1]		
Cholecystitis	1(0.5) [1]		
Subject With Fatal SAEs	0		

**Conclusions:**

See publication below

**Publications:**

Clotet B, Carmena J, Pulido F, Luque I., Rodríguez-Alcantara F. Adherence, quality of life, and general satisfaction with co-formulated zidovudine, lamivudine, and abacavir on antiretroviral-experienced patients. HIV Clin Trials 2004; 5(1):33-39.

Adherence to and general satisfaction with Trizivir' in HIV-1 patients B Clotet', F Pulido J Carmena' 'Germans Trias i Pujol, 6th International Congress on Drug Therapy in HIV Infection; Glasgow, Scotland. 2002 Nov 17

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