

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: AZL30004 (Extension Phase)
Title: A Phase IIIb/IV, Randomised, Open-Label, Multicentre Study to Evaluate the Efficacy, Safety and Tolerability of TRIZIVIR. plus Efavirenz (Quad) Over 72 Weeks Versus Quad Therapy for 48 Weeks Followed by TRIZIVIR Alone for 24 Weeks Versus Quad Therapy for a minimum of 24 Weeks Followed by TRIZIVIR Alone for 48 Weeks in HIV-Infected Antiretroviral Therapy Naïve Adults: Final 168 Week Analysis (Extension Phase).
Rationale: The Extension Phase of this study was designed to obtain long-term safety and efficacy data on the use of Trizivir (TZV) in already-suppressed patients. Subjects who successfully completed the original 72 weeks of the study, were still suppressed (<50 copies/mL), and remained on study drug were eligible to participate. All subjects were prescribed TZV alone and were followed-up for a further 96 weeks until Week 168.
Phase: IIIb/IV
Study Period: 05 November 2001 - 03 March 2006
Study Design: Phase IIIb/IV, Randomised, Open-Label, Multicentre Study
Centres: Fifty-five investigators in Europe enrolled subjects into this study
Indication: Human Immunodeficiency Virus Type 1 (HIV-1)
Treatment: All subjects in the Extension Phase were prescribed TZV twice daily (BID) alone for a further 96 weeks. TZV is a fixed dose triple combination tablet composed of abacavir sulfate (ABC, 300mg), lamivudine (3TC, 150mg) and zidovudine (ZDV, 300mg).
Objectives: All objectives for the extension phase of the study are classified as secondary objectives: To assess the antiviral efficacy of TRIZIVIR (TZV; abacavir sulfate, lamivudine, and zidovudine tablets) following 120 and 168 weeks of induction maintenance with a TZV-containing regimen in patients who remained suppressed over the first 72 weeks of treatment, within baseline HIV-1 ribonucleic acid (RNA). To assess the safety of TZV following 120 and 168 weeks of induction maintenance with a TZV-containing regimen in patients who remained suppressed over the first 72 weeks of treatment.
Primary Outcome/Efficacy Variable: The results of this endpoint were described in the 72-week CTR Summary for AZL30004. All endpoints for the Extension Phase of the study were classified as secondary objectives, as detailed below.
Secondary Outcome/Efficacy Variables: The secondary endpoints that pertained to the first 72 weeks of the study are presented in the 72-week CTR Summary. The secondary endpoints for the Extension Phase of the study were: Proportion of subjects with HIV-1 RNA <400 copies/mL and <50 at Week 120 and Week 168 for Extension Phase population, missing/switch=failure and observed analysis Measured values in plasma HIV-1 RNA over time Measured values and actual changes from baseline in CD4+ cell counts over time Incidence and frequency of HIV disease progression Incidence of adverse events and laboratory abnormalities between Week 72, Week 120 and Week 168. Development of genotypic/phenotypic markers associated with reduced viral sensitivity to antiretroviral agents in subjects receiving study drug who fail to respond to treatment.
Statistical Methods: No formal statistical hypothesis testing was performed. Only descriptive methods were used in the analysis. The proportions of subjects with plasma HIV-1 RNA <50 copies/mL were tabulated by visit using Switch/Missing = Failure (S/M=F) and Observed analyses. The proportions of subjects with plasma HIV-1 RNA <400 copies/mL were also summarized by visit using S/M=F and Observed analysis strategies. Study outcomes at week 168 were summarized using S/M=F analysis.
Study Population: HIV-1-infected male or female subjects ≥16 years (or ≥18 years in some

countries according to local regulatory requirements) were enrolled in the initial study. The main eligibility criterion was no prior experience of antiretroviral therapies (<2 weeks of prior therapy with any licensed or investigational protease inhibitor [PI], nucleoside reverse transcriptase inhibitor [NRTI] or nucleotide RTI and naïve to non-nucleoside reverse transcriptase inhibitors [NNRTIs]). There was no plasma HIV-1 RNA or CD4+ cell count cut-off for entry into this study. Subjects were stratified based on their Baseline plasma HIV-1 RNA as <100,000 copies/mL or ≥ 100,000 copies/mL. To be eligible for the Extension Phase of the study, subjects successfully completed the original 72 weeks of the study, were still suppressed (plasma HIV-1 RNA <50 copies/ml), and remained on study drug.

		All Subjects
Number of Subjects who Entered the Extension Phase		156
Completed, n (%)		123 (79%)
Total Number Subjects Withdrawn, N (%)		33 (21%)
Withdrawn due to Adverse Events, n (%)		6 (18%)
Withdrawn due to Serious Adverse Events, n (%)		3 (21%)
Withdrawn due to Insufficient Viral Load Response, n (%)		5 (15%)
Withdrawn for other reasons, n (%)		22 (66%)
Demographics		All Subjects
N (Safety Population)		156
Females: Males		36 : 120
Mean Age, years (SD)		37.2 (9.52)
Race, White, n (%)		112 (72%)
Efficacy Results: Plasma HIV-1 RNA <50 copies/mL through Week 168 Extension Phase (All Subjects)		
Week	S/M=F Analysis n/N (%)	Observed Analysis n/N (%)
Week 2	11/156 (7%)	11/148 (7%)
Week 4	26/156 (17%)	26/154 (17%)
Week 8	62/156 (40%)	62/152 (41%)
Week 12	100/156 (64%)	100/149 (67%)
Week 16	132/156 (85%)	132/155 (85%)
Week 24	151/156 (97%)	151/155 (97%)
Week 36	150/156 (96%)	150/155 (97%)
Week 48	152/156 (97%)	152/153 (99%)
Week 60	148/156 (95%)	148/152 (97%)
Week 72	146/156 (94%)	146/154 (95%)
Week 84	126/156 (81%)	126/135 (93%)
Week 96	135/156 (87%)	136/148 (92%)
Week 108	126/156 (81%)	126/139 (91%)
Week 120	129/156 (83%)	129/136 (95%)
Week 132	115/156 (74%)	117/130 (90%)
Week 144	113/156 (72%)	114/121 (94%)
Week 156	109/156 (70%)	111/125 (89%)
Week 168	101/156 (65%)	102/115 (89%)
N = Number of subjects in the population n = Number of subjects with HIV-1 RNA <50 copies/mL % = Percentage of subjects with HIV-1 RNA <50 copies/mL		

Plasma HIV-1 RNA <400 copies/mL through Week 168			
Week	S/M=F Analysis n/N (%)		Observed Analysis n/N (%)
Week 2	62/156 (40%)		62/148 (42%)
Week 4	96/156 (62%)		96/154 (62%)
Week 8	137/156 (88%)		137/152 (90%)
Week 12	147/156 (94%)		147/149 (99%)
Week 16	155/156 (99%)		155/155 (100%)
Week 24	154/156 (99%)		154/155 (99%)
Week 36	155/156 (99%)		155/155 (100%)
Week 48	153/156 (98%)		153/153 (100%)
Week 60	151/156 (97%)		151/152 (99%)
Week 72	154/156 (99%)		154/154 (100%)
Week 84	133/156 (85%)		133/135 (99%)
Week 96	143/156 (92%)		144/148 (97%)
Week 108	136/156 (87%)		136/139 (98%)
Week 120	134/156 (86%)		134/136 (99%)
Week 132	124/156 (79%)		127/130 (98%)
Week 144	118/156 (76%)		119/121 (98%)
Week 156	118/156 (76%)		120/125 (96%)
Week 168	109/156 (70%)		110/115 (96%)
N = Number of subjects in the population n = Number of subjects with HIV-1 RNA <50 copies/mL % = Percentage of subjects with HIV-1 RNA <50 copies/mL			
Summary of Change from Baseline in Plasma HIV-1 RNA (log₁₀ copies/mL) at Week 168			
	N=156		
HIV-1 RNA (log₁₀ copies/mL)	Overall	Baseline plasma HIV- 1 RNA <100,000 copies/mL	Baseline plasma HIV- 1 RNA ≥100,000 copies/mL
n	115	71	44
Mean (sd)	-3.009 (0.8038)	-2.552 (0.6429)	-3.746 (0.3721)
Median (IQ range)	-3.009 (-3.672, -2.565)	-2.741 (-3.009, -2.218)	-3.780 (-4.030, -3.565)
Summary of Change from Baseline in CD4+ Cell Counts (cells/mm³) at Week 168			
	N=156		
CD4+ Cell Counts (cells/mm³)	Overall	Baseline plasma HIV- 1 RNA <100,000 copies/mL	Baseline plasma HIV- 1 RNA ≥100,000 copies/mL
n	111	70	41
Mean (sd)	298.8 (206.34)	255.2 (162.96)	373.2 (249.53)
Median (IQ range)	258.0 (174.0, 372.0)	235.5 (128.0, 325.0)	291.0 (205.0, 481.0)
HIV Disease Progressions			All Subjects N=156
Number of subjects progressing from CDC Class A to CDC Class C			1 (<1%)
Number of subjects progressing from CDC Class B to CDC Class C			0 (0%)
Number of subjects progressing from CDC Class C to new CDC Class C			0 (0%)
Number of subjects progressing from CDC Class A, B or C to Death			1 (<1%)
Total number of subjects progressing to CDC Class C or Death			2 (1%)
Note: Treatment emergent condition in the extension phase is a condition with onset date on or after Week 72.			

Safety Results: Adverse events were collected during the Treatment Period. The most frequent 10 treatment emergent adverse events are presented below for All Phases combined and for the Extension Phase only.

Treatment Emergent Adverse Event	All Phases N=156	
Ten Most Frequent Adverse Events -O n-Therapy	n (%)	
Subjects with any AE(s), n(%)	145 (93%)	
Nausea	51 (33%)	
Diarrhoea	37 (24%)	
Insomnia	37 (24%)	
Dizziness	33 (21%)	
Fatigue	31 (20%)	
Vomiting	29 (19%)	
Headache	26 (17%)	
Pyrexia	23 (15%)	
Rash	23 (15%)	
Depression	22 (14%)	
Treatment Emergent Adverse Event	Extension Phase N=156	
Ten Most Frequent Adverse Events -O n-Therapy	n (%)	
Subjects with any AE(s), n(%)	114 (73%)	
Nasopharyngitis	13 (8%)	
Diarrhoea	11 (7%)	
Influenza	11 (7%)	
Nausea	10 (6%)	
Upper respiratory tract infection	10 (6%)	
Cough	8 (5%)	
Pharyngolaryngeal pain	7 (4%)	
Pyrexia	7 (4%)	
Influenza like illness	6 (4%)	
Depression	6 (4%)	
Serious Adverse Events - On-Therapy, n (%)	All Phases N=156	Extension Phase N=156
Subjects with non-fatal SAEs, n (%) drug-related [n (%)]	31 (20%) [5 (3%)]	16 (10%) [2 (1%)]

Myocardial infarction	2 (1%) [1 (<1%)]	2 (1%) [1 (<1%)]
Cellulitis	1 (<1%) [0]	1 (<1%) [0]
Tooth infection	1 (<1%) [0]	1 (<1%) [0]
Bladder cancer	1 (<1%) [0]	1 (<1%) [0]
Hodgkin's disease	1 (<1%) [0]	1 (<1%) [0]
Non-Hodgkin's lymphoma	1 (<1%) [0]	1 (<1%) [0]
Papillary thyroid cancer	1 (<1%) [0]	1 (<1%) [0]
Hemiparesis	1 (<1%) [0]	1 (<1%) [0]
Acute myocardial infarction	1 (<1%) [0]	1 (<1%) [0]
Lung disorder	1 (<1%) [0]	1 (<1%) [0]
Appendicitis perforated	1 (<1%) [0]	1 (<1%) [0]
Haematuria	1 (<1%) [0]	1 (<1%) [0]
Renal failure	1 (<1%) [0]	1 (<1%) [0]
Neutropenia	1 (<1%) [1 (<1%)]	1 (<1%) [1 (<1%)]
Pain	1 (<1%) [0]	1 (<1%) [0]
Pyrexia	1 (<1%) [0]	1 (<1%) [0]
Skin laceration	1 (<1%) [0]	1 (<1%) [0]
Lymphoedema	1 (<1%) [0]	1 (<1%) [0]
Appendicitis	1 (<1%) [0]	0 [0]
Condyloma acuminatum	1 (<1%) [0]	0 [0]
Gangrene	1 (<1%) [0]	0 [0]
Gastroenteritis	1 (<1%) [0]	0 [0]
Pneumonia	1 (<1%) [0]	0 [0]
Pyelonephritis	1 (<1%) [0]	0 [0]
Salpingitis	1 (<1%) [0]	0 [0]
Tubo-ovarian abscess	1 (<1%) [0]	0 [0]
Upper respiratory tract infection	1 (<1%) [0]	0 [0]
Fibroadenoma of breast	1 (<1%) [0]	0 [0]
Headache	1 (<1%) [0]	0 [0]
Hypertonia	1 (<1%) [0]	0 [0]
Ischaemic stroke	1 (<1%) [0]	0 [0]
Asthma	1 (<1%) [0]	0 [0]
Pleurisy	1 (<1%) [0]	0 [0]
Abdominal pain	1 (<1%) [0]	0 [0]
Diarrhoea	1 (<1%) [0]	0 [0]
Depression	1 (<1%) [1 (<1%)]	0 [0]
Suicide attempt	1 (<1%) [0]	0 [0]
Retinal detachment	1 (<1%) [0]	0 [0]
Neutrophil count decreased	1 (<1%) [1 (<1%)]	0 [0]
White blood cell count decreased	1 (<1%) [1 (<1%)]	0 [0]
Rhabdomyolysis	1 (<1%) [0]	0 [0]
Abortion spontaneous	1 (<1%) [1 (<1%)]	0 [0]
Subjects with fatal SAEs, n (%)		
Completed suicide	1 (<1%) [0]	1 (<1%) [0]

Conclusion:

During this extension phase study, the majority of subjects had plasma HIV-1 RNA <50 copies/mL at Week 168 (101/156 subjects; 65%) for the S/M=F analysis. The proportions of subjects with plasma HIV-1 RNA <50 copies/mL were decreased from Week 72 (94%) through Week 168 (65%), the majority of this decline being comprised of study withdrawal due to adverse events or administrative reasons. During this extension phase study, 114 subjects reported adverse events, with the most commonly reported adverse events were nasopharyngitis, diarrhoea, and influenza; sixteen serious adverse events were reported, one fatality was reported.

Publications:

Randomised comparison of maintenance therapy with trizivir [TZV] + efavirenz [EFV] vs TZV in naive HIV-1 infected subjects: TIME study De Wit, S.; Johnson, M.; Gazzard, B.; Bergmann, J. F.; Reynes, J.; Estrada, V.; Castagna, A., and Rockstroh, J., 7th International Congress on Drug Therapy in HIV Infection; Glasgow; Scotland. 2004 Nov 14 INDUCTION THERAPY WITH TRIZIVIR (ZIDOVUDINE/LAMIVUDINE/ABACAVIR) [TZV] PLUS EFAVIRENZ [EFV]: TIME STUDY (AZI-30004) RESULTS AT 24 WEEKS.

Johnson M., De Wit S. Gazzard B. Bergmann JI. Reynes J. Estrada V. Castagna A. Rockstroh J. , 9th European AIDS Conference (EACS) 1st EACS Resistance and Pharmacology Workshop; Warsaw; Poland. 2003 Oct 25 Efficacy and safety of AZT/3TC/ZDV (Trizivir) maintenance treatment after first line quadruple induction therapy- interim 24 weeks: data from AZLF3004/TRISUD.

Jean-Marie Ragnaud, Benedicte Delmas Herve Gallais Dominique Peyramond' Henri Laurichesse Pierre Dellamonica jean-Luc PL-Ilegrid ThierryAllegre NathalieAudebert' JacquesReyn on behalf of InfectioSud group, 6th International Congress on Drug Therapy in HIV Infection; Glasgow; Scotland. 2002 Nov 17.

Date Updated: 21-Dec-2006