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.: COL40263
Title: A Pilot, Open-Label, Multi-Center Study to Evaluate the Efficacy and Safety of a Once-Daily Regimen of Trizivir in Combination with Tenofovir Disoproxil Fumarate in Antiretroviral Therapy-Naïve Subjects with Viral Loads ≥30,000 copies/mL
Rationale: Once-daily antiretroviral regimens have been demonstrated to provide durable virologic suppression. Once daily dosing and low pill burden are believed to facilitate medication adherence, which in turn positively affects virologic and immunologic efficacy. This study was designed to evaluate a class-sparing treatment strategy consisting of a simplified, once-daily regimen of four nucleoside/nucleotide reverse transcriptase inhibitors consisting of tenofovir (one tablet daily) and (abacavir/lamivudine/zidovudine [TZV], two tablets daily) for 48 weeks in antiretroviral-naïve HIV-infected adults.
Phase: Pilot
Study Period*: July 2002 to August 2004
Study Design: Single-arm, non-randomized, open-label, observational, multicenter design
Centres: 11 U.S. outpatient sites
Indication: HIV-1 infection
Treatment: Abacavir/lamivudine/zidovudine 300/150/300 mg (TZV) QD + tenofovir 300 mg (TDF) once daily (QD) for 48 weeks. For subjects meeting criteria for protocol-defined confirmed virologic non-response, incomplete response, or rebound, lopinavir/ritonavir 400/100 BID could be substituted for tenofovir QD.
Objectives: To evaluate the antiretroviral efficacy, safety, and tolerability of a once-daily combination of abacavir/lamivudine/zidovudine (two tablets daily) plus tenofovir (one tablet daily) in antiretroviral-naïve, HIV-infected adults with entry plasma HIV-1 RNA ≥30,000 copies/mL.
Primary Outcome/Efficacy Variable: Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Weeks 24 Proportion of subjects with grade 3 or 4 adverse events and laboratory toxicities
Secondary Outcome/Efficacy Variable(s): Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 Proportion of subjects with plasma HIV-1 RNA <400 copies/mL at Weeks 24 and 48 Change from baseline in plasma HIV-1 RNA at Weeks 24 and 48 Change from baseline in CD4+ and CD8+ cell counts at Weeks 24 and 48 Change from baseline in resistance mutations (genotype) in virologic non-responders Change from baseline in phenotypic resistance in virologic non-responders Change from baseline in percent of body fat distribution and bone density Change from baseline in mitochondrial DNA Self-reported adherence Fasting lipids (total cholesterol, LDL, HDL, triglycerides)
Statistical Methods: The sample size of 125 subjects was based on practical rather than statistical considerations since this was a pilot study. A total of 100 evaluable subjects by week 48 was desired. The primary efficacy population was the intent-to-treat (ITT) population, which consisted of all enrolled subjects. The primary population for safety analyses was the safety population, which consisted of all subjects who had at least one dose of any study drug. The primary efficacy analysis was based on the observed rate in the ITT population (ITT: OBS), where only observed data was included in the estimation of the response rate. The Missing=Failure rate was also provided (ITT: M=F) for supportive purposes; this rate imputes failures for missing assessments or assessments taken after switching from baseline regimen. Summaries of the proportion of subjects with HIV-1 RNA <400 copies/mL and the proportion of subjects with HIV-1 RNA <50 copies/mL were also provided by the baseline HIV-1 RNA strata: <100,000 copies/mL or ≥100,000 copies/mL. Descriptive statistics were provided for genotypic and phenotypic resistance data, body fat distribution, bone mineral density and mitochondrial DNA data. Self-reported adherence was assessed by the Patient Medication Adherence Questionnaire (PMAQ-3W). Perfect adherence to each study drug/regimen was measured by the 4 questions in Part 2 of PMAQ-3W. A “no” to all 4 questions constitutes a perfect adherence score to the study drug or regimen. The number and percent of subjects with perfect adherence scores were summarized.

Study Population: Male and female subjects were included if they were ≥18 and ≤65 years of age with HIV-1 documented by ELISA and confirmed by Western blot, positive HIV-1 blood culture, positive serum antigen, or plasma viremia; were antiretroviral-naïve; provided written informed consent; had an entry plasma HIV RNA ≥30,000 copies/mL within 21 days prior to study enrollment; did not have an AIDS-defining illness within 30 days of screening. Women able to conceive had to have a negative serum pregnancy test at screening and agree to use adequate birth control until 2 weeks after study completion or discontinuation from the study.		
	TZV QD + TDF QD		
Number of Subjects:			
Planned, N	125		
Entered, N	123		
Completed, n (%)	71 (58)		
Total Number Subjects Withdrawn, N (%)	52 (42)		
Withdrawn due to Adverse Events, n (%)	14 (27)		
Withdrawn due to Lack of Efficacy, n (%)	12 (23)		
Withdrawn for other reasons, n (%)	26 (21) [Ψ]		
[Ψ]Other reasons as indicated on the case report form (CRF): lost to follow up (n=13), consent withdrawn (n=5), protocol violation (n=5), other (n=3: moved; incarceration; lack of efficacy)			
Demographics	**TZV QD + TDF QD**		
N (ITT)	123		
Females: Males, n (%)	21 (17): 102 (83)		
Age, years Median (range) mean (SD)	 38 (20 – 57) 38 (8.4)		
Black, n (%) White, n (%)	50 (41) 57 (46)		
CDC Classification, n (%) A or asymptomatic B or symptomatic C or AIDS-defining illness	 91 (74) 20 (16) 12 (10)		
HIV Risk Factor, n (%)[ξ] Homosexual contact Heterosexual contact Injectable drug use Occupational exposure Transfusion Other [ξ] Subjects could indicate more than one risk factor	 79 (64) 40 (33) 6 (5) 2 (2) 2 (2) 1 (<1)		
Baseline HIV RNA, median log_{10} c/mL (range) Subjects with <100,000 c/mL, n (%) Subjects with ≥100,000 c/mL, n (%)	5.08 (4.08 – 6.53) 51 (41) 72 (59)		
Baseline CD4+, median cells/mm^3 (range) Subjects with <200 cells/mm^3, n (%) Subjects with ≥200 cells/mm^3, n (%)	222 (20 – 857) 55 (45) 68 (55)		
Primary Efficacy Results:			
	TZV QD+ TDF QD		
	All subjects (N=123)	Subjects with baseline HIV RNA <100,000 c/mL (N=51)	Subjects with baseline HIV RNA ≥100,000 c/mL (N=72)
HIV RNA <50 c/mL, n/N (%) of subjects (ITT: OBS)			
Week 24	67/95 (71)	34/41 (83)	33/54 (61)
	TZV QD + TDF QD (N=123)		

Proportion of subjects with grade 3 or 4 adverse events, n (%) (Safety)	18 (15)		
Proportion of subjects with any grade 3 or 4 laboratory toxicities, n (%) (Safety)	14 (11)		
Secondary Outcome Variables:			
	TZV QD+ TDF QD		
	All subjects (N=123)	Subjects with baseline HIV RNA <100,000 c/mL (N=51)	Subjects with baseline HIV RNA ≥100,000 c/mL (N=72)
HIV RNA <50 c/mL, n/N (%) of subjects (ITT: OBS)			
Week 48	51/68 (75)	24/28 (86)	27/40 (68)
HIV RNA <50 c/mL, n/N (%) of subjects (ITT: M=F)			
Week 24	67/123 (54)	34/51 (67)	33/72 (46)
Week 48	51/123 (41)	24/51 (47)	27/72 (38)
HIV RNA <400 c/mL, n/N (%) of subjects (ITT: OBS)			
Week 24	82/95 (86)	37/41 (90)	45/54 (83)
Week 48	63/68 (93)	26/28 (93)	37/40 (93)
HIV RNA <400 c/mL, n/N (%) of subjects (ITT: M=F)			
Week 24	82/123 (67)	37/51 (73)	45/72 (63)
Week 48	63/123 (51)	26/51 (51)	37/72 (51)
	TZV QD + TDF QD		
Change in plasma HIV-1 RNA from baseline (log10 copies/mL), median (range) (ITT: OBS)			
Week 24, n=95	-3.283 (-4.572 – 0.301)		
Week 48, n=68	-3.299 (-4.719 – 0.865)		
Change in CD4+ count from baseline (cells/mm^3), median (range) (ITT: OBS)			
Week 24, n=94	94.5 (-273 – 524)		
Week 48, n=67	127 (-173 – 515)		
Change in CD8+ count from baseline (cells/mm^3), median (range) (ITT: OBS)			
Week 24, n=94	-55 (-1827 – 1022)		
Week 48, n=67	-109 (-1586 – 813)		
Reverse Transcriptase mutations at last visit (>24 weeks) for protocol-defined virologic non-responders, n/N (%)			
Wild type	4/14 (29)		
K65R only	1/14 (7)		
M184V only	1/14 (7)		
≥1 TAMS	3/14 (21)		
≥1 TAMS + K65R	1/14 (7)		
≥1 TAMS + M184R	4/14 (29)		
Phenotypic susceptibility at last visit (>24 weeks) for protocol-defined virologic non-responders, n/N (%)			
Wild type to all ARTs	8/13 (62)		
Resistant to ABC, 3TC, and ZDV	1/13 (8)		
Resistant to ABC and 3TC	2/13 (15)		

Resistant to 3TC only	2/13 (15)
Percent change in fat from baseline by body region and visit, median (range)	
Arm: Week 24, n=11	4.15 (-26.35 – 88.98)
Week 48, n=7	9.46 (-11.46 – 98.54)
Leg: Week 24, n=11	9.11 (-17.01 – 69.71)
Week 48, n=7	11.36 (-23.97 – 76.43)
Head: Week 24, n=11	2.77 (-6.80 – 12.72)
Week 48, n=7	6.15 (-7.04 – 12.40)
Trunk: Week 24, n=11	0.75 (-19.13 – 41.71)
Week 48, n=7	13.52 (-18.20 – 76.74)
Percent change in bone mineral density from baseline by body region and visit, median (range)	
Hip: Week 24, n=10	-1.34 (-9.40 – 0.20)
Week 48, n=6	-2.88 (-5.42 – 0.57)
Spine: Week 24, n=10	-2.36 (-6.81 – 1.83)
Week 48, n=6	0.83 (-6.99 – 4.36)
Change in mitochondrial DNA PBMC levels from baseline, median (range)	
Week 48, n=16	0.02 (-297.36 – 1713.58)
Overall perfect adherence as measured by PMAQ-3W (Part 2), n/N (%)	
TZV	83/114 (72)
TDF	81/113 (71)
TZV/TDF	81/113 (71)
Change in Fasting Lipid Profile from Baseline	
Total cholesterol (mg/dL), median (range)	
Week 8, n=93	-9.0 (-68 – 46)
Week 24, n=81	-8.0 (-71 – 56)
Week 48, n=60	-9.0 (-62 – 77)
LDL cholesterol (mg/dL), median (range)	
Week 8, n=88	-8.5 (-59 – 43)
Week 24, n=81	-9.0 (-61 – 43)
Week 48, n=59	-9.0 (-51 – 50)
HDL cholesterol (mg/dL), median (range)	
Week 8, n=89	1.0 (-16 – 20)
Week 24, n=81	-1.0 (-25 – 19)
Week 48, n=59	1.0 (-25 – 25)
Triglycerides (mg/dL), median (range)	
Week 8, n=93	0 (-180 – 203)
Week 24, n=81	-4.0 (-182 – 214)
Week 48, n=60	-3.5 (-168 – 162)
Safety Results: An AE was defined as any untoward medical occurrence (any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a subject that was temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events were classified as serious if they resulted in death, were life-threatening, required hospitalization, resulted in significant disability, were a congenital anomaly, or were a hypersensitivity reaction to abacavir.	
	TZV QD + TDF QD (N=123)
Most Frequent Adverse Events – On-Therapy	**n (%)**

Subjects with any grade 3 or grade 4 AE(s)	18 (15)
Drug hypersensitivity	5 (4)
Nausea	2 (2)
Arthritis	1 (<1)
Anemia	1 (<1)
Blood potassium decreased	1 (<1)
Convulsion	1 (<1)
Dysphagia	1 (<1)
Dyspnea	1 (<1)
Eye pain	1 (<1)
Fatigue	1 (<1)
Hepatic enzyme increased	1 (<1)
Kaposi's sarcoma	1 (<1)
Lipase increased	1 (<1)
Liver function test abnormal	1 (<1)
Pain in extremity	1 (<1)
Pneumocystis carinii pneumonia	1 (<1)
Sepsis	1 (<1)
Vascular pseudoaneurysm	1 (<1)
Serious Adverse Events - On-Therapy n (%) [n **considered by the investigator to be related to study medication]**	
	TZV QD + TDF QD (N=123)
Subjects with any SAEs, n (%)	16 (13)
Drug hypersensitivity	8 (7) [8]
Convulsion	2 (2) [0]
Pneumonia	2 (2) [0]
Anemia	1 (<1) [0]
Dehydration	1 (<1) [0]
Duodenitis	1 (<1) [0]
Dysphagia	1 (<1) [0]
Esophageal ulcer	1 (<1) [0]
Gastritis	1 (<1) [0]
Injury	1 (<1) [0]
Loss of consciousness	1 (<1) [0]
Pneumocystis carinii pneumonia	1 (<1) [0]
Pyrexia	1 (<1) [0]
Reflux esophagitis	1 (<1) [0]
Sepsis	1 (<1) [0]
Skin laceration	1 (<1) [0]
Unstable angina	1 (<1) [0]
Vascular pseudoaneurysm	1 (<1) [0]

Conclusion: See publications below.

Publications:

Elion R., et al. COL40263: Resistance and Efficacy of Once-daily Trizivir and Tenofovir DF in Antiretroviral Naïve Subjects. 11th Conference on Retroviruses & Opportunistic Infections. San Francisco, CA, February 8-11, 2004. Oral M-138.

DeJesus E., et al. Week 24 Analysis of Once-Daily Trizivir (TZV) and Tenofovir DF (DF) in Antiretroviral Naive Subjects (COL40263). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington DC, October 20-November 2, 2004. Poster 2950.

Cohen, C., et al. Week 48 Analysis of Once-Daily (QD) Trizivir (TZV) and Tenofovir DF (TDF) in Antiretroviral Naïve Subjects (COL40263). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC,

December 16-19, 2005. Poster H-521.

Elion, R., et al. Selection of HIV Reverse Transcriptase (RT) Thymidine Analogue Mutations (TAMS) Rather than K65R is the Preferred Route of Resistance Seen in Patients with Virologic Failure on Once-Daily (QD) Trizivir (TZV) and Tenofovir (TDF). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC December 16-19, 2005. Poster H-1068.

DeJesus, E., et al. Week 24 Analysis of Once-Daily (QD) Trizivir (TZV) and Tenofovir DF (TDF) in Antiretroviral-naïve Subjects (COL40263). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC, October 30 –November 2, 2004: Poster H-456.

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