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Study No.: COL30336	
Title: A Phase IV, Open-Label, Multicenter Study of the Efficacy and Safety of Quadruple Combination Antiretroviral Therapy with <i>COMBIVIR</i> (Lamivudine 150mg/Zidovudine 300mg) BID, <i>ZIAGEN</i> (Abacavir) 300mg BID, and <i>SUSTIVA</i> (Efavirenz) 600mg QD for 24 Weeks, Followed by Therapy with the Triple Nucleoside Combination Tablet (Abacavir 300mg/Lamivudine 150mg/Zidovudine 300mg [<i>TRIZIVIR</i>]) BID plus <i>SUSTIVA</i> (Efavirenz) 600mg QD for 24 Weeks in HIV-Infected Adults.	
Rationale: COL30336 was designed and conducted to gain experience with the compact quadruple regimen of zidovudine/lamivudine fixed dose combination (COM)/abacavir/efavirenz for 24 weeks, followed by abacavir/zidovudine/lamivudine fixed dose combination (TZV)/efavirenz for the subsequent 24 weeks, in antiretroviral-naïve, HIV-infected adults.	
Phase: IV	
Study Period: October 1999 to October 2001	
Study Design: Single-arm, open-label, multicenter study design.	
Centers: 5 outpatient sites (US).	
Indication: Human immunodeficiency virus type 1 (HIV-1) infection	
Treatment: COM BID +abacavir 300mg BID + efavirenz 600mg QD for 24 weeks, followed by TZV BID + efavirenz 600mg QD for an additional 24 weeks.	
Objectives: To evaluate virologic and immunologic efficacy, tolerability, adherence, and resistance patterns associated with abacavir/lamivudine/zidovudine BID + efavirenz in the treatment of antiretroviral-naïve, HIV-infected adult adults with entry HIV RNA $\geq 1,000$ copies/milliliter (c/mL). The effect of treatment on T-cell receptor excision circles (TREC), phenotypic and/or genotypic resistance, and adherence to treatment were also assessed.	
Primary Outcome/Efficacy Variable: - Viral load response (HIV-1 RNA in plasma)	
Secondary Outcome/Efficacy Variable(s): - Safety and tolerability - CD4+ lymphocyte response - Immune reconstitution (naïve CD4+ T-cells, renormalization of CD4+ T-cell receptor repertoire, and TREC) - Development of clinical AIDS-defining illness - Development of phenotypic and/or genotypic resistance - Adherence to quadruple HAART regimen (Patient Medication Adherence Questionnaire (PMAQ7 version 1.1) and pill counts)	
Statistical Methods: The sample size was based on practical rather than statistical considerations. Data analysis pertained to the intent-to-treat (ITT) population. Four types of analysis were done: ITT, missing/switch = failure (ITT, M=F); ITT, last-observation-carried-forward (ITT, LOCF); ITT observed, switch = included (ITT:S=I); and as-treated. Means (\pm standard deviations), medians, and 25th and 75th percentiles were calculated for plasma HIV-1 RNA levels and CD4+ cell counts. These statistics were also calculated for change from baseline of plasma HIV-1 RNA levels and CD4+ cell counts.	
Study Population: Subjects could be included if they were male or non-pregnant females ≥ 18 years of age with HIV-1 infection documented by HIV-1 antibody enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot detection of HIV-1 antibody, positive HIV-1 blood culture, positive HIV serum antigen, or plasma viremia; had a screening plasma HIV-1 RNA value $\geq 1,000$ c/mL within 21 days prior to study drug administration; were naïve to treatment with NNRTIs, PIs, abacavir, and either lamivudine or zidovudine or had ≤ 7 total days of prior treatment with NRTIs; laboratory values within normal limits; not receiving immunomodulating drugs, cytotoxic chemotherapy, or radiation; had no serious medical condition that would compromise safety. Women of childbearing potential had to have a negative serum pregnancy test (β -HCG) within 21 days of study drug administration and be using adequate contraception	
Demographics of study subjects , ITT	COM/abacavir/efavirenz or TZV/efavirenz
Mean Age (sd), yrs	38.8 (9.0)

Sex, n (%)	
Female	5 (13)
Male	33 (87)
Race, n (%)	
Black	16 (42)
White	15 (39)
Mean weight, kg	79.6
CDC Classification, n (%)	
Asymptomatic or lymphadenopathy	35 (92)
Symptomatic, not AIDS	3 (8)
AIDS	0
Non-CDC HIV-associated conditions, n (%)	
No	37 (97)
Yes	1 (3)
Median baseline HIV-1 RNA, log ₁₀ c/mL (range)	5.12 (3.42-6.15)
No. (%) of subjects with HIV-1 RNA ≥100,000 c/mL	25 (66)
Median baseline CD4+ cell count, cells/mm ³ (range)	284.75 (7.00-865.00)
Disposition during study	COM/abacavir/efavirenz or TZV/efavirenz
Number of Subjects	
Planned, N	40
Randomised, N	38
Completed, n (%)	29 (76.3)
Total Number Subjects Withdrawn, N (%)	9 (23.7)
Withdrawn due to Adverse Events n (%)	2 (5.3)
Withdrawn due to Lack of Efficacy n (%) (Virologic failure)	1 (2.6)
Withdrawn for other reasons n (%)	6 (15.8)
Primary Efficacy Results	COM/abacavir/efavirenz or TZV/efavirenz
HIV-1 RNA <400 c/mL, n/N (%) of subjects (ITT:S=I)	
Baseline	0/38 (0)
Week 2	13/38 (34.21)
Week 4	19/36 (52.78)
Week 8	31/37 (83.78)
Week 12	32/34 (94.12)
Week 16	33/34 (97.06)
Week 24*	33/35 (94.29)
Week 32	32/32 (100.00)
Week 40	31/31 (100.00)
Week 48	29/29 (100.00)
* Primary efficacy results are for 24-week period; data after Week 24 were considered secondary efficacy results	
Secondary Efficacy Results	COM/abacavir/efavirenz or TZV/efavirenz
HIV-1 RNA <50 c/mL, n/N (%) of subjects (ITT:S=I)	
Baseline	0/38 (0)
Week 2	3/38 (7.89)
Week 4	5/36 (13.89)
Week 8	9/37 (24.32)
Week 12	16/34 (47.06)
Week 16	24/34 (70.59)
Week 24	28/35 (80.00)
Week 32	30/32 (93.75)
Week 40	29/31 (93.55)

Week 48	27/29 (93.10)	
HIV-1 RNA <3 c/mL, n/N (%) of subjects (ITT:S=I)		
Baseline	0/0 (0)	
Week 2	0/3 (0)	
Week 4	4/5 (80.00)	
Week 8	6/9 (66.67)	
Week 12	7/16 (43.75)	
Week 16	10/23 (43.48)	
Week 24	16/27 (59.26)	
Week 32	24/30 (80.00)	
Week 40	20/29 (68.97)	
Week 48	16/27 (59.26)	
CD4 cell count, median cells/mm ³ (ITT: S=I)		
	Subjects with baseline HIV-1 RNA <100,000 c/mL (N=13)	Subjects with baseline HIV-1 RNA ≥100,000 c/mL (N=13)
Baseline	376.50	238.50
Week 4	394.00	342.00
Week 8	406.00	389.00
Week 16	487.00	306.00
Week 24	365.50	339.00
Week 32	365.00	318.00
Week 40	521.00	378.00
Week 48	481.50	390.00
Increase above baseline in entire population at Week 48	172	
TRECs, median excision circles per 100,000 cells (ITT: S=I)		
Baseline	203.0	
Week 12	620.5	
Week 24	657.0	
Week 48	1267.5	
Development of phenotypic (PT) and/or genotypic (GT) resistance*	GT K103N at week 8; M184V/M184M, K103N at week 12	PT High-level NNRTI resistance; no NRTI resistance
*For the one subject who was classified as a virologic failure (occurred at week 16)		
Adherence		
Median by self-report	100% at all assessments	
% of subjects who took all HIV drugs during previous 7 days		
Week 2	74%	
Week 48	92%	
* Adherence was defined as the number of self-reported doses taken out of the total number of self-reported doses prescribed.		
Safety Results:		
Most Frequent Adverse Events – On-Therapy		
Subjects with any AE(s), n(%)	n (%)	
Nausea	17 (45)	

Dreams	13 (34)
Malaise and fatigue	10 (26)
Hypnagogic effects	9 (24)
Dizziness	8 (21)
Sleep disorders	8 (21)
Depressive disorders	8 (21)
Headache	7 (18)
Musculoskeletal pain	6 (16)
Diarrhea	5 (13)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	8 (21)
Allergic reaction to medicinal substance (ABC Hypersensitivity)	3 (8) [3]
Temperature regulation disturbance	1 (3) [0]
Suicide or attempted suicide	2 (5) [2]
Depressive disorders	1 (3) [1]
Fluid disturbances	1 (3) [0]
Appendicitis	1 (3) [0]
Pneumonia	1 (3) [0]
Urinary tract obstructions	1 (3) [0]
Subjects with fatal SAEs, n (%)	0

Conclusion: See publications below.

Publication:

Ruane P., et. al. Compact Quadruple Therapy with the Lamivudine/Zidovudine Combination Tablet Plus Abacavir and Efavirenz, Followed by the Lamivudine/Zidovudine/Abacavir Triple Nucleoside Tablet Plus Efavirenz in Treatment-Naïve HIV-Infected Adults. HIV Clinical Trials 2003, 4(4), 231-243.

Ruane P., et al. The PI-sparing compact quad regimen of *Combivir*/abacavir/efavirenz (COM/ABC/EFV) is potent and well-tolerated in naive subjects with high viral loads: 24-week data. In: 2001 Spring Practice and Research Forum of the American College of Clinical Pharmacy. Salt Lake City, UT, April 22–25, 2001. Poster 47E.

Parenti D., Ruane P., et. al. The Compact Quad, *Combivir*/Abacavir/Efavirenz (COM/ABC/EFV) Preliminary 48-Wk Result (COL30336). In: 39th Annual Meeting of the Infectious Diseases Society of America. San Francisco, CA, October 25-28, 2001. Poster 697.

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