



FINAL CLINICAL STUDY REPORT

Study Title: Combination of Efavirenz and Truvada[®] (The **COMET** Study): A Phase 4 Evaluation of Switching from Twice Daily Zidovudine and Lamivudine (Combivir[®]) to a Simplified, Once-Daily Regimen of Co-formulated Emtricitabine and Tenofovir Disoproxil Fumarate (Truvada[®]), in Virologically Suppressed, HIV- Infected Patients Taking Efavirenz

Name of Test Drug: Emtricitabine/Tenofovir Disoproxil Fumarate Tablet

Indication: HIV-1 Infection

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Study No.: GS-US-164-0107

Phase of Development: Phase 4

IND No.: Not applicable
EudraCT No.: Not applicable

Study Start Date: 14 October 2004 (First Subject Screened)
Study End Date: 21 February 2006 (Last Subject Observation)

Principal or Coordinating Investigator: Name: Edwin DeJesus, MD, FACP
Affiliation: Orlando Immunology Center

Gilead Responsible Medical Monitor: John Flaherty, PharmD

Report Date: 23 August 2006

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: **Combination of Efavirenz and Truvada[®] (The COMET Study):** A Phase 4 Evaluation of Switching from Twice Daily Zidovudine and Lamivudine (Combivir[®]) to a Simplified, Once-Daily Regimen of Co-formulated Emtricitabine and Tenofovir Disoproxil Fumarate (Truvada[®]), in Virologically Suppressed, HIV- Infected Patients Taking Efavirenz

Investigators: Multicenter; refer to Appendix 4 for a complete listing of investigators.

Study Centers: 71 centers in the United States enrolled subjects in the study; however, data from 70 centers are included in the analyses because data are not available from one center.

Publications:

DeJesus E, McDonald C, Garcia F, Shamblaw D, Ecker J, Ebrahimi R, and Flaherty J, for the COMET Team. Effects of Switching from Fixed Dose Zidovudine/Lamivudine (CBV) to Fixed Dose Tenofovir DF/Emtricitabine (TVD): Maintenance of Virologic Suppression and Other Benefits. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16–19, 2005; Washington, D.C., USA. Poster Number H-517.

DeJesus E, McDonald C, Garcia F, Shamblaw D, Ecker J, Ebrahimi R, and Flaherty J, for the COMET Team. Effects of Switching from Fixed Dose Zidovudine/Lamivudine (CBV) to Fixed Dose Tenofovir DF/Emtricitabine (TVD): Maintenance of Virologic Suppression and Other Benefits. 15th Annual Canadian Conference on HIV/AIDS Research, May 25–28, 2006; Québec City, Canada. Oral Presentation 214.

Ruane P, Sharma S, DeJesus E, Ravishankar J, Khanlou H, Ebrahimi R, Ecker J, Flaherty J, and the COMET Study Group. Improved Virologic Suppression after HIV-Infected Patients are Switched from Fixed Dose Zidovudine/Lamivudine to Fixed Dose Tenofovir DF/Emtricitabine. 10th European AIDS Conference (EACS), November 17–20, 2005; Dublin, Ireland. Poster Number PE7.3/5.

Study Period:

14 October 2004 (First subject screened)
21 February 2006 (Last subject observation)

Phase of Development: Phase 4

STUDY SYNOPSIS (CONTINUED)

Objectives:

The objective of this study was to characterize the risks, effectiveness, and benefits of switching from a Combivir (BID) /efavirenz (QD) regimen to an all-QD regimen of Truvada[®]/efavirenz.

Methodology: A prospective, single-arm, open-label, switch study in treatment-experienced HIV-1–infected, virologically suppressed subjects on a stable regimen of efavirenz taken with Combivir, who have evidence of adverse clinical or laboratory effects associated with Combivir or who might benefit from a simplified, once-daily antiretroviral regimen regardless of Combivir tolerability status.

Number of Subjects (Planned and Analyzed):

Planned: 400
Analyzed: 402

Diagnosis and Main Criteria for Inclusion: HIV-1-infected, virologically suppressed subjects on a stable regimen of efavirenz taken with Combivir

Duration of Treatment: 24 weeks

Test Product, Dose, Mode of Administration, and Batch No.:

Emtricitabine/tenofovir DF 200 mg/300 mg fixed-dose combination oral tablet
Batch numbers: V304B2, V308B2, V403B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: None.

Criteria for Evaluation:

Efficacy: antiviral efficacy as assessed by HIV-1 RNA suppression and CD4+ cell count

Safety: safety and tolerability

Outcome Measures: satisfaction with the treatment regimen and quality of life

Statistical Methods:

Efficacy: Overall response to treatment was assessed as the proportion of subjects with HIV-1 RNA < 400 copies/mL at Week 24. The change in CD4+ cell count from baseline through Week 24 was evaluated. The efficacy (e.g., HIV-1 RNA maintenance) data summary includes all subjects who took at least one dose of study drug and had post-baseline data.

Safety: Adverse events and clinical laboratory tests were assessed. The safety data summary includes all subjects who took at least one dose of study drug and have post-baseline data.

Outcome Measures: The QoL and Patient Adherence, Treatment Satisfaction, and Symptoms Questionnaire data were summarized by cohort and overall.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS:

A total of 411 subjects were enrolled; 402 subjects were evaluable for safety, and 401 subjects were evaluable for efficacy. Thirty subjects were discontinued prematurely. Subjects in this study were predominantly male (83%); 67% were white and 23% were black; median age was 43 years. Median duration of prior Combivir treatment was 3.9 years.

Efficacy Results: For the MITT analysis set (missing = failure), 85% of subjects had HIV-1 RNA < 400 copies/mL and 71% of subjects had HIV-1 RNA < 50 copies/mL at Week 24. Mean change in CD4+ cell count from baseline to Week 24 was 15 cells/mm³, which was statistically significant (p = 0.02).

Safety Results: The regimen of emtricitabine/tenofovir DF (200 mg/300 mg once daily) + efavirenz (600 mg once daily) was well tolerated in this study population of HIV-1 infected subjects. AEs reported in > 2% of subjects were nausea (5%), diarrhea (5%), upper respiratory tract infection (4%), headache (3%), and insomnia (3%). Grade 3 or 4 laboratory abnormalities occurred in 1% of subjects: neutropenia (2 subjects), thrombocytopenia (1 subject), and increased triglycerides (2 subjects). One death due to suicide occurred during the study. SAEs were reported for 17 subjects; 10 subjects discontinued early from the study due to adverse events. There was no evidence of a clinically significant effect on renal function, as measured by changes from baseline or maximum graded toxicity of serum creatinine and calculated creatinine clearance. The only renal and urinary AE that occurred in more than 1 subject was dysuria, which was reported in 2 subjects.

Outcome Measure Results: Satisfaction with treatment as assessed by subject-reported questionnaire (Patient Adherence, Treatment Satisfaction, and Symptoms Questionnaire), showed statistically significant improvement (p < 0.001) in all 5 categories of treatment satisfaction. For all 20 subject-reported symptoms, the presence or absence of each symptom improved from baseline to Week 24, and for 17 of 20 symptoms, the improvement was statistically significant (p < 0.05).

In the SF-36 Health Survey, mean positive changes were seen for the physical and mental composite scores and for all domains except vitality. For components of physical health, statistically significant changes from baseline to Week 24 (p < 0.05) were seen for 3 of 4 domains as well as the physical health composite score. For components of mental health, no statistically significant changes from baseline were seen.

STUDY SYNOPSIS (CONTINUED)

CONCLUSIONS:

- In virologically controlled, treatment-experienced subjects (HIV-1 RNA < 400 copies/mL), switching from the twice-daily regimen of Combivir + efavirenz to a once-daily (two-tablet) regimen of emtricitabine/tenofovir DF + efavirenz was associated with maintenance of virologic suppression and immune function.
- The regimen of emtricitabine/tenofovir DF and efavirenz was well tolerated; there was no evidence of any clinically significant toxicity related to the use of emtricitabine/tenofovir DF. The results of key safety assessments (decreases in fasting lipids and increase in hemoglobin) support the established safety profile of the emtricitabine/tenofovir DF and efavirenz regimen.
- The results of several outcome measures demonstrated a high level of satisfaction with the regimen compared with baseline and improvement of self-reported symptoms following 24 weeks of treatment. Adherence to the regimen was high (mean adherence of 98% by pill count and $\geq 95\%$ adherence in 86% of subjects by questionnaire).