



INTERIM CLINICAL STUDY REPORT

Study Title: A Phase 3, Randomized, Open-Label, Multicenter Study of the Treatment of Antiretroviral-Naive, HIV-1 Infected Subjects Comparing Tenofovir Disoproxil Fumarate and Emtricitabine in Combination with Efavirenz Versus Combivir[®] (lamivudine/zidovudine) and Efavirenz

Name of Test Drugs: Emtricitabine, Tenofovir Disoproxil Fumarate

Indication: Treatment of HIV Infected Patients

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

Study No.: GS-01-934

Phase of Development: Phase 3

IND No.: 52,849

EudraCT No.: Not Allocated to Date

Study Start Date: 29 July 2003 (First Patient Screened)

Study End Date: 11 February 2005 (Last Patient Observation, Study Ongoing)

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Report Date: 29 April 2005

Previous Report Date(s): 04 March 2004 (Interim Summary Report)
25 May 2004 (Interim Report)
28 September 2004 (Interim Synopsis Report)

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was performed in compliance 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: A Phase 3, Randomized, Open-Label, Multicenter Study of the Treatment of Antiretroviral-Naive, HIV-1 Infected Subjects Comparing Tenofovir Disoproxil Fumarate and Emtricitabine in Combination with Efavirenz Versus Combivir® (lamivudine/zidovudine) and Efavirenz

Investigators: Multicenter

Study Centers: 70 centers in the United States and Europe screened at least one patient

Publications:

Arribas JR, DeJesus E, Campo R, Jemsek J, Gallant JE, Gazzard B, et al. The combination of tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) has significantly greater response vs. fixed dose zidovudine/lamivudine (CBV) and EFV in antiretroviral naïve patients: a 24 week preliminary analysis [poster]. 7th International Congress on Drug Therapy in HIV Infection; 2004 November 14–18; Glasgow, UK.

Gazzard BG, DeJesus E, Campo R, Jemsek J, Gallant JE, Arribas JR, et al. The combination of tenofovir DF (TDF), emtricitabine (FTC) and Efavirenz (EFV) has significantly greater response vs fixed dose zidovudine/lamivudine (CBV) and EFV in antiretroviral naïve patients: a 24 week preliminary analysis [oral presentation]. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2004 October 30–November 2; Washington, DC, USA. Oral Number H-1137c.

Arribas J, Pozniak AL, Gallant JE, DeJesus E, Campo R, Gazzard B, et al. Superior outcome for tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) compared to fixed dose zidovudine/lamivudine (CBV) and EFV in antiretroviral naive patients [oral presentation]. 18th International Conference on Antiviral Research; 2005 April 10–14; Barcelona, Spain.

SYNOPSIS (CONTINUED)

Study Period:

29 July 2003 (First patient screened)

11 February 2005 (Last patient observation for Week 48 analysis, study ongoing)

Phase of Development: Phase 3**Objectives:**

The primary objective of this study was as follows:

- To assess noninferiority of emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) in combination with efavirenz relative to Combivir in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive patients, determined by the achievement and maintenance of confirmed HIV-1 RNA < 400 copies/mL through Week 48, as defined by the United States (US) Food and Drug Administration (FDA) time-to-loss-of-virologic-response (TLOVR) algorithm.

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of the two treatment regimens through 96 weeks of drug exposure.
- To assess noninferiority of emtricitabine and tenofovir DF in combination with efavirenz relative to Combivir in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive patients, determined by the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Week 48, as defined by the FDA TLOVR algorithm, and the achievement and maintenance of confirmed HIV-1 RNA < 400 and < 50 copies/mL through Week 96, as defined by the FDA TLOVR algorithm.
- To assess the incidence of hyperpigmentation in both treatment groups.
- To evaluate the effect of dosing emtricitabine and tenofovir DF without regard to meals.

Methodology: Randomized, open-label, parallel, multicenter, active-controlled study to assess the noninferiority of two treatment regimens, efavirenz + emtricitabine + tenofovir DF versus efavirenz + Combivir with 1:1 randomization. Patients were stratified on the basis of screening CD4 cell count (< or \geq 200 cells/mm³).

Number of Patients (Planned and Enrolled):

Planned: 500 (250 patients in each treatment group)

Enrolled: 517

Diagnosis and Main Criteria for Inclusion: Antiretroviral-naive, HIV-1 infected patients with plasma HIV-1 RNA concentrations > 10,000 copies/mL

SYNOPSIS (CONTINUED)

Duration of Treatment: 96 weeks

Test Product, Dose, Mode of Administration, and Batch No.: Efavirenz 600 mg once daily (Lot Nos. TP203A, ERC232A, and ERF412A) for oral administration, emtricitabine 200 mg once daily (Lot Nos. W302A1, W303A1, W304A1, and W304A1 A), and tenofovir DF 300 mg once daily (Lot Nos. J109B1, J205B2, J206B2, J206B2 A, and J305B1). Nevirapine 200 mg twice daily (according to the nevirapine prescribing information found in Appendix 9 of the protocol) could replace efavirenz in the event of efavirenz-associated central nervous system (CNS) toxicity.

Reference Therapy, Dose, Mode of Administration, and Batch No.: Efavirenz 600 mg once daily (Lot Nos. TP203A, ERC232A, and ERF412A) for oral administration and Combivir (lamivudine/zidovudine; Lot Nos. 3ZP0638, 3ZP1843, and 3ZP2427) 150/300 mg twice daily. Nevirapine 200 mg twice daily (according to the nevirapine prescribing information found in Appendix 9 of the protocol) could replace efavirenz in the event of efavirenz-associated CNS toxicity.

Criteria for Evaluation:

Efficacy: Achievement and maintenance of confirmed HIV-1 RNA < 400 copies/mL and < 50 copies/mL through Week 48 and Week 96, as defined by the FDA TLOVR algorithm.

Safety: Adverse events, clinical laboratory tests

Statistical Methods:

Efficacy: The primary efficacy endpoint for this 96-week study was the achievement and maintenance of confirmed HIV-1 RNA concentrations < 400 copies/mL through Week 48, as defined by the FDA TLOVR algorithm. The noninferiority of emtricitabine and tenofovir DF in combination with efavirenz relative to Combivir in combination with efavirenz with respect to this endpoint was assessed using a two-sided 95% confidence interval for the baseline CD4 stratum-weighted difference in the proportions of patients who achieved and maintained confirmed HIV-1 RNA < 400 copies/mL at Week 48 (emtricitabine + tenofovir DF group minus Combivir group). The emtricitabine + tenofovir DF group was declared noninferior to the Combivir group if the lower confidence bound was ≥ -0.13 . The modified intent-to-treat analysis set, which excluded patients with baseline nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance, was used in this analysis.

Safety: The safety endpoints for the Week 48 interim analysis included treatment-emergent adverse events, deaths and serious adverse events, adverse events leading to discontinuation of study drug, and clinical laboratory toxicities.

The primary safety and efficacy analysis, which is presented in this clinical study report, was conducted upon completion of 48 weeks on study by the last enrolled patient. The end-of-study analysis will be conducted when the last enrolled patient completes 96 weeks on study.

SYNOPSIS (CONTINUED)

SUMMARY – RESULTS:

Efficacy Results: In the primary efficacy analysis of the modified ITT analysis set (which excluded patients who were treatment-experienced or had primary NNRTI resistance mutations at baseline), the proportion of patients who achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48, as defined by the TLOVR algorithm, was significantly higher for the emtricitabine + tenofovir DF group relative to the Combivir group (84% vs. 73%; $p = 0.002$). The difference in proportions, weighted by baseline CD4 cell count stratification, between the emtricitabine + tenofovir DF group and the Combivir group was 11%, and the 95% confidence interval (CI) was 4% to 19%. Similarly, the proportion of patients in the ITT analysis set who achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48, as defined by the TLOVR algorithm, was significantly higher for the emtricitabine + tenofovir DF group relative to the Combivir group (81% vs. 71%; $p = 0.005$; stratum-weighted difference, 11%; 95% CI, 3% to 18%). Because the 95% confidence intervals (MITT and ITT) for the treatment effect lie entirely above the limit of ≥ -0.13 required for demonstration of noninferiority and, furthermore, lie entirely above zero, and because the p -values ($p = 0.002$, MITT; $p = 0.005$, ITT) support rejection of the null hypothesis of no difference between the treatment groups, it is concluded that the efavirenz + emtricitabine + tenofovir DF regimen is superior to the efavirenz + Combivir regimen.

Superiority of the efavirenz + emtricitabine + tenofovir DF regimen was also demonstrated in the analysis of the proportion of patients who achieved and maintained plasma HIV-1 RNA < 50 copies/mL through Week 48, as defined by the TLOVR algorithm (80% for the emtricitabine + tenofovir DF group vs. 70% for the Combivir group; $p = 0.021$; stratum-weighted difference, 9%; 95% CI, 2% to 17%). Similarly, for the ITT analysis set, the proportion of patients who achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48, as defined by the TLOVR algorithm, was significantly higher for the emtricitabine + tenofovir DF group compared with the Combivir group (77% vs. 68%; $p = 0.034$, stratum-weighted difference, 9%; 95% CI, 1% to 16%).

The results of the analysis of time to loss of virologic response and time to pure virologic failure further confirm the superiority of the efavirenz + emtricitabine + tenofovir DF regimen compared with the efavirenz + Combivir regimen. Kaplan-Meier estimates for the proportions of patients with loss of virologic response and the proportions of patients with pure virologic failure by Week 48 were significantly lower for the emtricitabine + tenofovir DF group compared with the Combivir group when the LLQ for HIV-1 RNA was 400 copies/mL (19% vs. 30% for loss of virologic response, $p = 0.003$; 9% vs. 16% for pure virologic failure, $p = 0.026$). Similarly, when the LLQ for HIV-1 RNA was 50 copies/mL, the Kaplan-Meier estimates for the proportions of patients with loss of virologic response and the proportions of patients with pure virologic failure by Week 48 were lower for the emtricitabine + tenofovir DF group compared with the Combivir group (23% vs. 32% for loss of virologic response, $p = 0.026$; 16% vs. 24% for pure virologic failure, $p = 0.063$).

SYNOPSIS (CONTINUED)

Efficacy Results (continued): Mean decreases in plasma HIV-1 RNA from baseline to Week 48 were similar between the two treatment groups (3.31 log₁₀ copies/mL for the emtricitabine + tenofovir DF group and 3.26 log₁₀ copies/mL for the Combivir group).

Mean increases in CD4 cell count from baseline to Week 48 were significantly greater for the emtricitabine + tenofovir DF group than for the Combivir group (190 vs. 158 cells/mm³, p = 0.002).

Subgroup analysis demonstrated that in patients with baseline HIV-1 RNA > 100,000 copies/mL or with baseline CD4 cell counts ≥ 200 cells/mm³, the proportion of patients achieving and maintaining plasma HIV-1 RNA < 400 copies/mL through Week 48 was significantly higher in the emtricitabine + tenofovir DF group than in the Combivir group (p = 0.016 and p = 0.017, respectively). For subgroups of patients with baseline HIV-1 RNA < 100,000 copies/mL or with baseline CD4 cell counts < 200 cells/mm³, the difference between treatment groups in the proportion of patients achieving and maintaining plasma HIV-1 RNA < 400 copies/mL favored the efavirenz + emtricitabine + tenofovir DF regimen, although statistical significance was not attained.

At Week 48, genotypic and phenotypic resistance analyses were performed for all patients who had confirmed plasma HIV-1 RNA > 400 copies/mL by Week 48 or early study drug discontinuation, corresponding to 5% of patients in the emtricitabine + tenofovir DF group and 10% of patients in the Combivir group. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed and it occurred as a single mutation or in combination with the M184V/I mutation, which causes reduced susceptibility to both emtricitabine and lamivudine. The M184V/I mutation was the most common NRTI-associated mutation, and it developed in 1% of the patients in the emtricitabine + tenofovir DF group and in 3% of patients in the Combivir group. The M184V/I mutation occurred predominantly in combination with efavirenz resistance. One patient in the Combivir group developed a thymidine analog-associated mutation, and no patient in either treatment group developed the K65R mutation, which is associated with reduced susceptibility to tenofovir DF. No novel patterns of mutations associated with reduced phenotypic susceptibility to either emtricitabine or tenofovir DF were detected in any patient.

Safety Results: Up to Week 48, the overall incidence of treatment-emergent AEs was similar between the two treatment groups. Treatment-emergent AEs were reported in 94% of patients in the emtricitabine + tenofovir DF group and 95% of patients in the Combivir group. The most frequently reported AEs in the emtricitabine + tenofovir DF group were dizziness (28%), nausea (24%), and diarrhea (20%). In the Combivir group, the most frequently reported AEs were nausea (31%), dizziness (28%), and insomnia (17%). In both treatment groups, the most frequently reported treatment-emergent AEs assessed as related to study drugs were nausea (11% in the emtricitabine + tenofovir DF group and 26% in the Combivir group) and diarrhea (6% in both groups).

SYNOPSIS (CONTINUED)

Safety Results (continued): Anemia (including decreased hemoglobin) was reported as a study drug-related AE for 6% of patients in the Combivir group and was not reported in any patients in the emtricitabine + tenofovir DF group. Anemia, the only treatment-emergent Grade 3 or 4 AE reported in more than 1% of patients in either treatment group, was reported in 4% of patients in the Combivir group and no patients in the emtricitabine + tenofovir DF group. Of the ten Grade 3 or 4 anemia events, 7 were reported as SAEs.

The overall incidence of treatment-emergent SAEs was similar between the two treatment groups (8% in the emtricitabine + tenofovir DF group and 9% in the Combivir group). Anemia was the only SAE considered by the investigator to be possibly or probably related to study drugs (3% of patients in the Combivir group and no patients in the emtricitabine + tenofovir DF group). Up to the cutoff for this interim report, 3 deaths have occurred in this study; one death (emtricitabine + tenofovir DF group) was due to Kaposi sarcoma, another death (Combivir group) was due to progressive multifocal leukoencephalopathy, and the third death (Combivir group) was due to a suspected drug overdose. All deaths were assessed by the investigator as not related to study drugs.

Adverse events leading to study drug discontinuation occurred in a significantly smaller percentage of patients in the emtricitabine + tenofovir DF group compared with the Combivir group (4% vs. 9%, $p = 0.019$). The most frequently occurring AE leading to study drug discontinuation was anemia, including decreased hemoglobin (6% of patients in the Combivir group and no patients in the emtricitabine + tenofovir DF group).

Adverse events of skin hyperpigmentation were reported for 16 patients (11 in the emtricitabine + tenofovir DF group and 5 in the Combivir group). Of the 16 cases of hyperpigmentation, 3 cases (2 in the emtricitabine + tenofovir DF group and 1 in the Combivir group) were assessed by a dermatologist as not related to study drugs. Of the remaining 13 hyperpigmentation cases, 5 were assessed by a dermatologist as related or probably related to study drugs (4 in the emtricitabine + tenofovir DF group and 1 in the Combivir group), 6 were pending dermatologist assessment, and 2 were not assessable because the patient refused dermatologist evaluation. All hyperpigmentation events (except one Grade 2 event in the Combivir group, pending assessment) were of Grade 1 severity.

The incidence of bone fractures at Week 48 was similar between the two treatment groups (3 in the emtricitabine + tenofovir DF group and 2 in the Combivir group). All fractures were considered by the investigator to be unrelated to any of the study drugs, and no change in study regimen dosing was made as a result of any fracture.

SYNOPSIS (CONTINUED)

Safety Results (continued): There was no evidence of a tenofovir DF effect on renal function, as measured by changes from baseline or maximum graded toxicity of serum creatinine or serum phosphorus concentrations. No confirmed Grade 3 or 4 serum creatinine elevation (2 consecutive values at least 1 day apart) was reported. No patient experienced a Grade 3 or 4 serum phosphorus decrease. No patient discontinued study drugs because of a renal AE.

The mean increases in fasting total serum cholesterol and fasting serum low-density lipoprotein concentrations from baseline to Week 48 were significantly smaller for the emtricitabine + tenofovir DF group relative to the Combivir group ($p < 0.001$ and $p = 0.013$, respectively).

CONCLUSIONS:

- In antiretroviral treatment-naïve HIV-1 infected patients treated for 48 weeks, the once-daily regimen of emtricitabine, tenofovir DF, and efavirenz administered without regard to food demonstrated superior antiviral efficacy relative to the regimen of Combivir and efavirenz.
- Through 48 weeks, development of resistance to efavirenz was the most common form of resistance that developed in both treatment groups of the study. Resistance to emtricitabine (M184V/I mutation) developed infrequently, and no resistance to tenofovir DF (K65R mutation) developed. No novel mutations resulting in phenotypic resistance to either tenofovir DF or emtricitabine developed by Week 48.
- The once-daily regimen of emtricitabine, tenofovir DF, and efavirenz demonstrated a preferential safety profile compared with the Combivir plus efavirenz regimen, as evidenced by the significantly lower rate of study drug discontinuation due to an AE. In the emtricitabine and tenofovir DF group, there were few reports of hyperpigmentation, and no effect on renal function was observed.