



INTERIM CLINICAL STUDY SYNOPSIS (96 WEEKS)

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:	Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate
Indication:	HIV-1 Infection
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 Applicable
Study Start Date:	29 July 2003 (First Patient Screened)
Study End Date:	24 January 2006 (Last Patient Observation, Study Ongoing)
Principal Investigator:	Name: Anton Pozniak, MD, FRCP Affiliation: Chelsea and Westminster Hospital, London
Gilead Responsible Medical Monitor:	Name: Andrew Cheng, MD, PhD Telephone: (650) 522-5658 Fax: (650) 522-5595
Report Date:	27 June 2006
Synopsis Date:	25 March 2008
Previous Report Dates:	29 April 2005 (Week 48 Interim Clinical Study Report) 28 September 2004 (Week 24 Interim Synopsis Report) 25 May 2004 (Median 24-Week Interim Report) 04 March 2004 (Median 16-Week Interim Summary Report)

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: 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:

Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, emtricitabine, efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006;354 (3):251-60.

Fisher M, Gallant JE, DeJesus E, Pozniak A, Lu B, Enejosa J, et al. Response to antiretroviral therapy with tenofovir DF (TDF) and emtricitabine (FTC) versus zidovudine/lamivudine (Combivir, CBV) in combination with efavirenz (EFV) in hepatitis C (HCV)/HIV co-infected antiretroviral-naive patients [poster number 23]. 2nd International Workshop on HIV and Hepatitis Co-Infection; 2006 January 12-14; Amsterdam, The Netherlands.

Arribas JR, Gallant JE, DeJesus E, Pozniak A, Lu B, Enejosa J, et al. Response to antiretroviral therapy with tenofovir DF (TDF) and emtricitabine (FTC) versus zidovudine/lamivudine (Combivir, CBV) in combination with efavirenz (EFV) in hepatitis C (HCV)/HIV co-infected antiretroviral-naive patients [poster number PE13.2/16]. 10th European AIDS Conference (EACS); 2005 November 17-20; Dublin, Ireland.

Pozniak A, Gallant J, DeJesus E, Arribas JR, Lu B, McColl D, et al. Superior outcome for tenofovir DF and emtricitabine compared to fixed dose zidovudine/lamivudine in antiretroviral-naive HIV-infected patients: a 48-week analysis [poster number PE7.3/14]. 10th European AIDS Conference (EACS); 2005 Nov 17-20; Dublin Ireland.

McColl DJ, Margot NA, Lu B, Cheng AK, Miller MD. Lack of resistance to tenofovir DF at week 48 and impact of baseline NNRTI resistance mutations on treatment response in study 934 [poster number PE7.3/16]. 10th European AIDS Conference (EACS); 2005 November 17-20; Dublin, Ireland.

STUDY SYNOPSIS (CONTINUED)

Publications (continued):

Pozniak AL, Gallant JE, DeJesus E, Campo R, Gazzard B, Arribas JR, et al. Superior outcome for tenofovir DF, emtricitabine and efavirenz compared to fixed dose zidovudine/lamivudine and EFV in antiretroviral naïve patients [oral presentation WeOa0202]. 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment; 2005 July 24-27; Rio de Janeiro, Brazil.

McCull DJ, Margot NA, Lu B, Cheng AK, Miller MD. Lack of resistance to tenofovir DF at week 48 and impact of baseline resistance mutations on treatment response in study 934 [poster TuPp0305]. 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment; 2005 July 24-27; Rio de Janeiro, Brazil.

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 naïve patients [oral presentation]. 18th International Conference on Antiviral Research; 2005 April 10–14; Barcelona, Spain.

Study Period:

29 July 2003 (First patient screened)

24 January 2006 (Last patient observation for Week 96 analysis, study ongoing)

Phase of Development: Phase 3

STUDY SYNOPSIS (CONTINUED)

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 144 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 and by the achievement and maintenance of confirmed HIV-1 RNA < 400 and < 50 copies/mL through Week 96 and through Week 144 (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); emtricitabine and tenofovir DF are dosed as the emtricitabine/tenofovir DF fixed-dose combination tablet during Weeks 96 through 144.

After completing 144 weeks of treatment with study drug, patients from both study arms will be given the option to roll over into a 96-week protocol extension and switch their treatment regimen to a fixed-dose, triple-combination formulation of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir DF 300 mg.

Number of Patients (Planned and Analyzed):

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

STUDY SYNOPSIS (CONTINUED)

Duration of Treatment: 240 weeks total: 144 weeks of the randomized treatment followed by 96 weeks of the fixed-dose, triple-combination formulation of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir DF 300 mg

Test Product, Dose, Mode of Administration, and Batch No.: Efavirenz 600 mg once daily, orally, without regard to meals (Lot Nos. TP203A, ERC232A, ERF412A, ESL421A, and ETA038A), emtricitabine 200 mg once daily, orally, without regard to meals (Lot Nos. W302A1, W303A1, W304A1, W304A1-A, W306A1, and W308A1), and tenofovir DF 300 mg once daily, orally, without regard to meals (Lot Nos. FBK248, J109B1, J205B2, J205B2_S, J206B2, J206B2-A, J206B2_S, J206B2-A_S, J305B1, J305B1_S, and J305B1-B); nevirapine 200 mg twice daily orally (according to the nevirapine prescribing information found in Appendix 10 of Protocol Amendment 3) could replace efavirenz in the event of efavirenz-associated central nervous system (CNS) toxicity

Because of a protocol deviation, one patient received emtricitabine 200 mg and tenofovir DF 300 mg as the fixed-dose combination (Lot No. V402B1) at the Week 84 visit instead of the Week 96 visit, as specified in the protocol.

Reference Therapy, Dose, Mode of Administration, and Batch No.: Efavirenz 600 mg once daily, orally, without regard to meals (Lot Nos. TP203A, ERC232A, ERF412A, ESL421A, and ETA038A) and Combivir (lamivudine/zidovudine) 150 mg/300 mg twice daily, orally, without regard to meals (Lot Nos. 3ZP0638, 3ZP1843, 3ZP2427, 4ZP6753, 5ZP4075, 5ZP8607, and R166903); nevirapine 200 mg twice daily orally (according to the nevirapine prescribing information found in Appendix 10 of Protocol Amendment 3) 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, Week 96, and Week 144, as defined by the FDA TLOVR algorithm

Safety: Adverse events, clinical laboratory tests

STUDY SYNOPSIS (CONTINUED)

Statistical Methods:

Efficacy: The primary efficacy endpoint for this 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 modified intent-to-treat (MITT) analysis set, which excluded patients with baseline nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance, was used in this analysis. Results of the primary efficacy analysis were presented in the Week 48 interim clinical study report (29 April 2005) and are not repeated in this synopsis report.

The secondary efficacy endpoints for this study included the achievement and maintenance of confirmed HIV-1 RNA concentrations < 50 copies/mL through Week 48 and the achievement and maintenance of confirmed HIV-1 RNA concentrations < 400 copies/mL and < 50 copies/mL through Week 96 and through Week 144, as defined by the FDA TLOVR algorithm. In addition to excluding patients with baseline NNRTI resistance (MITT), the Week 96 efficacy analysis set excluded Week 48 TLOVR responders who did not consent to continue the study after Week 48.

The noninferiority of emtricitabine and tenofovir DF in combination with efavirenz relative to Combivir in combination with efavirenz through 96 weeks was assessed using a two-sided 95% confidence interval for the baseline CD4+ cell count stratum-weighted difference in the proportions of patients who achieved and maintained confirmed HIV-1 RNA < 400 copies/mL and < 50 copies/mL at Week 96 (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 .

Safety: The safety endpoints for the Week 96 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 was presented in a previous interim clinical study report, was conducted upon completion of 48 weeks on study by the last enrolled patient. This interim synopsis report presents results of safety and efficacy analyses conducted after the last enrolled patient completed 96 weeks on study. The Week 144 analysis of efficacy and safety will be conducted after the last subject completes 144 weeks on study, and the Week 240 analysis of efficacy and safety will be conducted after the last subject completes 240 weeks on study.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS:

Efficacy Results: The demonstrated antiretroviral efficacy of the once-daily regimen of efavirenz + emtricitabine + tenofovir DF continued through 96 weeks of treatment. In the secondary efficacy analyses (Week 96 efficacy analysis set, N = 463 for HIV-1 RNA < 400 copies/mL), a significantly higher proportion of patients in the emtricitabine + tenofovir DF group compared with the Combivir group achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 96, as defined by the TLOVR algorithm (75% [173/232] vs. 62% [143/231], p = 0.004). The difference in proportions, weighted by baseline CD4+ cell count stratum, between the emtricitabine + tenofovir DF group and the Combivir group was 13%, and the 95% confidence interval (CI) was 4% to 21%. Because the 95% confidence interval for the treatment effect lies entirely above the limit of ≥ -0.13 required for demonstration of noninferiority and, furthermore, lies entirely above zero, and because the p-value (p = 0.004) supports rejection of the null hypothesis of no difference between the treatment groups, the efavirenz + emtricitabine + tenofovir DF regimen is concluded to be superior to the efavirenz + Combivir regimen.

Treatment responders included patients who substituted nevirapine for efavirenz because of efavirenz-related CNS toxicities, as permitted by the study protocol. In accordance with the statistical analysis plan, these protocol-allowed switches were not accounted as failures in the TLOVR analysis, unless they met other predefined criteria for TLOVR failure. Of the 11 of 255 patients (4%) in the emtricitabine + tenofovir DF group and 12 of 254 patients (5%) in the Combivir group who substituted nevirapine for efavirenz, all except one patient in each group switched because of efavirenz-related CNS toxicity; one patient in each group switched because of rash. Both patients who switched because of rash were TLOVR nonresponders. Of the patients who substituted nevirapine for efavirenz because of efavirenz-related CNS toxicities, three patients in each treatment group were classified as TLOVR responders; the remaining patients were nonresponders (two patients in the emtricitabine + tenofovir DF group and seven patients in the Combivir group) or were excluded from the TLOVR analysis because they (a) did not consent to continue the study after Week 48 (four patients in the emtricitabine + tenofovir DF group and one patient in the Combivir group) or (b) had baseline NNRTI resistance (one patient in the emtricitabine + tenofovir DF group), as described in the statistical methods.

The proportion of patients (Week 96 efficacy analysis set, N = 465 for HIV-1 RNA < 50 copies/mL) who achieved and maintained plasma HIV-1 RNA < 50 copies/mL through Week 96 (TLOVR algorithm) was 67% (156/232) for the emtricitabine + tenofovir DF group and 61% (142/233) for the Combivir group (p = 0.16; stratum-weighted difference, 6%; 95% CI, -2% to 15%).

STUDY SYNOPSIS (CONTINUED)

Efficacy Results (continued): Kaplan-Meier estimates for the proportions of patients with loss of virologic response and the proportions of patients with pure virologic failure by Week 96 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 (25% vs. 37% for loss of virologic response, overall $p = 0.003$; 9% vs. 17% for pure virologic failure, overall $p = 0.02$, MITT). Time to loss-of-virologic response for patients who achieved a confirmed virologic response (two consecutive HIV-1 RNA below 400 copies/mL) before study drug discontinuation, was the time to the earliest premature study regimen discontinuation or confirmed HIV-1 RNA above 400 copies/mL (two consecutive HIV-1 RNA ≥ 400 copies/mL or the last HIV-1 RNA ≥ 400 copies/mL followed by loss to follow-up). The time to pure virologic failure for patients who achieved a confirmed virologic response was the time to the earliest date of confirmed HIV-1 RNA above 400 copies/mL (two consecutive HIV-1 RNA ≥ 400 copies/mL, or the last HIV-1 RNA ≥ 400 copies/mL followed by premature study discontinuation).

Mean decreases in plasma HIV-1 RNA from baseline were sustained through Week 96 and were similar between the two treatment groups (3.30 \log_{10} copies/mL for the emtricitabine + tenofovir DF group and 3.25 \log_{10} copies/mL for the Combivir group).

Mean increases from baseline in CD4+ cell count observed at Week 48 continued through Week 96 and were significantly greater for the emtricitabine + tenofovir DF group than for the Combivir group (270 vs. 237 cells/mm³, $p = 0.036$).

In patients with high baseline plasma HIV-1 RNA concentrations ($> 100,000$ copies/mL) or high baseline CD4+ cell counts (≥ 200 cells/mm³), the proportions of patients achieving and maintaining plasma HIV-1 RNA < 400 copies/mL through Week 96 were significantly higher in the emtricitabine + tenofovir DF group than in the Combivir group ($p = 0.014$ and $p = 0.024$, respectively; Week 96 efficacy analysis set). For subgroups of patients with baseline HIV-1 RNA $\leq 100,000$ copies/mL or with baseline CD4+ cell counts < 200 cells/mm³, the differences between treatment groups in the proportions 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.

Through 96 weeks of this study, in which study drugs were administered without regard to food, treatment response rates (i.e., achievement and maintenance of confirmed plasma HIV-1 RNA concentrations < 400 copies/mL) among patients who responded to a dosing questionnaire were similar between those who reported routinely dosing the regimen of efavirenz, emtricitabine, and tenofovir DF with food, i.e., within 1 hour, and those who reported routinely dosing without food, i.e., at least 1 hour before or after (97% vs. 100%, respectively).

STUDY SYNOPSIS (CONTINUED)

Efficacy Results (continued):

Resistance Analyses

Subsequent to the 48-week analysis, eight additional patients (two patients in the emtricitabine + tenofovir DF group and six patients in the Combivir group) met resistance analysis criteria, i.e., had confirmed (on at least two consecutive visits) plasma HIV-1 RNA concentrations ≥ 400 copies/mL or early study discontinuation, by Week 96 and were analyzed for genotypic and phenotypic resistance using the PhenoSense GT Assay™ (Monogram Biosciences, Inc., South San Francisco). None of these eight patients had baseline NNRTI resistance. Virologic rebound, according to the FDA TLOVR algorithm, occurred for five of the six patients in the Combivir group and neither patient in the emtricitabine + tenofovir DF group.

Genotypic and phenotypic analyses were successful for seven of the eight patients; genotypic analysis for one patient in the Combivir group failed because of technical reasons. Of the two patients in the emtricitabine + tenofovir DF group, the virus developed efavirenz resistance (EFV-R) in one patient (G190A mutation alone) and remained wild-type in the other patient. Neither patient in the emtricitabine + tenofovir DF group developed either the K65R or the M184V mutation, selected by tenofovir DF or emtricitabine, respectively. Among the five Combivir patients for whom genotypic data were available, one patient developed EFV-R (K103N mutation alone), one patient developed M184V alone, one patient developed EFV-R (A98G, K103N, and V108V/I mutations) plus M184V (and a noncanonical mutation at codon 67 of reverse transcriptase [RT] and V118I), and in two patients, the virus remained wild-type. No Combivir patient developed a classical thymidine analog mutation (TAM; M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/R/N mutations in RT) selected by zidovudine. Phenotypic data were available for all seven patients for whom genotypic analysis was successful.

STUDY SYNOPSIS (CONTINUED)

Efficacy Results (continued): Overall in Study GS-01-934, more than twice as many patients in the Combivir group compared with the emtricitabine + tenofovir DF group met the criteria for resistance analysis by Week 96 (29 patients vs. 14 patients, respectively; $p = 0.017$, Fisher exact test). Genotypic analyses were obtained for all 14 patients in the emtricitabine + tenofovir DF group and 27 of 29 patients in the Combivir group. The proportion of patients who developed any resistance in the Combivir group (20/243, 8%) was double that observed in the emtricitabine + tenofovir DF group (10/244, 4%); however, the difference was not statistically significant ($p = 0.06$). Resistance to efavirenz (EFV-R) was the most common form of resistance that developed, occurring in 10 of 244 patients (4%) in the emtricitabine + tenofovir DF group and 18 of 243 patients (7%) in the Combivir group. The K103N mutation was the most common EFV-R mutation that developed and was detected in 23 of the 28 patients with EFV-R. Other observed EFV-R mutations included A98G, K101E, K103E, V108I/M, V179D, Y188H, G190A/S, P225H, and M230L. A significantly greater proportion of patients developed the M184V mutation in the Combivir group (9/243, 4%) compared with the emtricitabine + tenofovir DF group (2/244, 1%; $p = 0.036$). By Week 96, only one of 243 patients (< 1%) in the Combivir group had developed a classical TAM (K70K/R) and another patient in the Combivir group had developed a noncanonical mutation at codon 67 (D67D/G, along with the V118I mutation). The D67G mutation also developed as a mixture in one patient in the emtricitabine + tenofovir DF group at the time of the Week 48 analysis. No patient in the emtricitabine + tenofovir DF group developed the K65R mutation selected by tenofovir DF. The proportion of patients in whom HIV-1 remained wild-type was similar between the two groups.

STUDY SYNOPSIS (CONTINUED)

Safety Results: Through 96 weeks, treatment-emergent adverse events (AEs) were reported in 95% of patients in the emtricitabine + tenofovir DF group and 96% of patients in the Combivir group. The most frequently reported AEs in the emtricitabine + tenofovir DF group were dizziness (28%), diarrhea (26%), and nausea (25%). In the Combivir group, the most frequently reported AEs were nausea (32%), dizziness (28%), and insomnia (19%). The most frequently reported (in > 5% of patients in either treatment group) treatment-emergent AEs considered related to study drugs (i.e., emtricitabine, tenofovir DF, or Combivir) were nausea (12% in the emtricitabine + tenofovir DF group and 26% in the Combivir group), diarrhea (7% in both groups), vomiting (2% in the emtricitabine + tenofovir DF group and 7% in the Combivir group), fatigue (3% in the emtricitabine + tenofovir DF group and 6% in the Combivir group), and anemia (including decreased hemoglobin, no patients in the emtricitabine + tenofovir DF group and 6% of patients in the Combivir group). Anemia, the most frequently reported individual treatment-emergent Grade 3 or 4 AE, 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 serious adverse events (SAEs).

Treatment-emergent AEs were reported with similar frequency among all subgroups (sex, age, race) for both treatment groups. By subgroups, the most frequently reported treatment-emergent AEs for both treatment groups were nausea or diarrhea and dizziness.

The overall incidence of treatment-emergent SAEs was similar between the two treatment groups (10% in the emtricitabine + tenofovir DF group and 11% in the Combivir group). Treatment-emergent SAEs reported for more than one patient in either treatment group were nephrolithiasis, pneumonia, and anemia. Nephrolithiasis was reported for < 1% of patients (2/257) in the emtricitabine + tenofovir DF group and no patients in the Combivir group; neither event was considered by the investigator to be related to emtricitabine or tenofovir DF. Pneumonia was reported in < 1% of patients (2/257) in the emtricitabine + tenofovir DF group and < 1% of patients (1/254) in the Combivir group; none of these events was considered by the investigator to be related to emtricitabine, tenofovir DF, or Combivir. Anemia, reported in no patients in the emtricitabine + tenofovir DF group and 3% of patients (7/254) in the Combivir group, was the only SAE considered by the investigator to be possibly or probably related to treatment (i.e., Combivir).

Up to the cutoff for the 96-week analysis, four deaths (two in the emtricitabine + tenofovir DF group and two in the Combivir group) have occurred in this study. Of the two patients in the emtricitabine + tenofovir DF group, one died of sepsis due to invasive Kaposi sarcoma, and the other died of coma due to lung adenocarcinoma with cerebral metastasis. Of the two patients in the Combivir group, one died of progressive multifocal leukoencephalopathy due to AIDS and the other died because of a suspected heroin overdose. All deaths were assessed by the investigator as not related to any of the study drugs (i.e., emtricitabine, tenofovir DF, Combivir, efavirenz, or nevirapine).

STUDY SYNOPSIS (CONTINUED)

Safety Results (continued): Through 96 weeks, adverse events leading to discontinuation of study drug (i.e., emtricitabine, tenofovir DF, or Combivir) occurred in a significantly smaller percentage of patients in the emtricitabine + tenofovir DF group compared with the Combivir group (5% vs. 11%, $p = 0.008$). 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 led to substitution of nevirapine for efavirenz for 4% of patients (11/255) in the emtricitabine + tenofovir DF group and 5% of patients (12/254) in the Combivir group. The most common reason for substitution was efavirenz-associated central nervous system toxicity (10 of the 255 patients [4%] in the emtricitabine + tenofovir DF group and 11 of the 254 patients [4%] in the Combivir group), followed by rash (one patient in each group).

Adverse events of skin hyperpigmentation were reported for 19 patients (12 in the emtricitabine + tenofovir DF group and seven in the Combivir group). For six of the 19 patients (five in the emtricitabine + tenofovir DF group and one in the Combivir group), a dermatologist assessed the hyperpigmentation events as not related to study drugs. Of the remaining 13 patients, hyperpigmentation was assessed by a dermatologist as related or probably related to study drugs for nine patients (six in the emtricitabine + tenofovir DF group and three in the Combivir group), dermatologist assessment was pending for one patient, and three were not assessable because the patient refused dermatologist evaluation. One hyperpigmentation event in the Combivir group was of Grade 2 severity; all other hyperpigmentation events were Grade 1.

The incidence of bone fractures was lower in the emtricitabine + tenofovir DF group (4 events) than in the Combivir group (7 events). All fractures were considered by the investigator as not related to any of the study drugs, and no change in study regimen dosing was made as a result of any fracture.

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 (i.e., two consecutive values at least one 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.

STUDY SYNOPSIS (CONTINUED)

Safety Results (continued): Median changes from baseline to Week 96 in calculated creatinine clearance (Cockcroft-Gault method) were -1.53 mL/min for the emtricitabine + tenofovir DF group and -0.34 mL/min for the Combivir group. Median changes from baseline to Week 96 in estimated glomerular filtration rate (Modification of Diet in Renal Disease (MDRD) Study equation) were -1.68 mL/min/ 1.73 m² for the emtricitabine + tenofovir DF group and -1.08 mL/min/ 1.73 m² for the Combivir group.

The mean increases in fasting total serum cholesterol and fasting serum high-density lipoprotein concentrations from baseline to Week 96 were significantly smaller for the emtricitabine + tenofovir DF group relative to the Combivir group ($p < 0.001$ and $p = 0.022$, respectively).

The mean body composition in limb fat was significantly greater in the emtricitabine + tenofovir DF group compared with the Combivir group at Week 48 (8.95 vs. 6.92 kg, respectively; $p = 0.035$) and Week 96 (9.05 vs. 6.50 kg, respectively; $p < 0.001$). From Week 48 to Week 96, the mean body composition in limb fat increased significantly for the emtricitabine + tenofovir DF group (+0.74 kg, $p = 0.01$), but decreased significantly for the Combivir group (-0.77 kg, $p = 0.001$).

STUDY SYNOPSIS (CONTINUED)

CONCLUSIONS:

- In antiretroviral treatment-naive HIV-1 infected patients, the once-daily regimen of efavirenz, emtricitabine, and tenofovir DF administered without regard to food demonstrated potent and durable antiviral efficacy. At Week 96, 75% of patients in the emtricitabine + tenofovir DF group achieved and maintained confirmed HIV-1 RNA < 400 copies/mL compared with 62% of patients in the Combivir group ($p = 0.004$; stratum-weighted difference, 13%; 95% CI, 4% to 21%). Because the 95% confidence interval for the treatment effect lies entirely above the limit of ≥ -0.13 required for demonstration of noninferiority and, furthermore, lies entirely above zero, and because the p -value ($p = 0.004$) supports rejection of the null hypothesis of no difference between the treatment groups, the efavirenz + emtricitabine + tenofovir DF regimen is concluded to be superior to the efavirenz + Combivir regimen. Resistance to efavirenz was the most common form of resistance to develop. Resistance to emtricitabine (M184V/I mutation) developed infrequently, and no resistance to tenofovir DF (K65R mutation) developed.
- Immunologic benefit was also demonstrated with increases in CD4+ cell count from baseline to Week 48, which continued through Week 96 to means of 270 cells/mm³ for the emtricitabine + tenofovir DF group compared with 237 cells/mm³ for the Combivir group ($p = 0.036$).
- The once-daily regimen of efavirenz, emtricitabine, and tenofovir DF continued to be well tolerated through 96 weeks and demonstrated a preferential safety profile compared with the efavirenz plus Combivir regimen, as evidenced by the significantly lower rate of study drug discontinuation due to an adverse event. In the emtricitabine + tenofovir DF group, no effect on renal function or evidence of bone toxicity was observed, and there were few reports of hyperpigmentation. Treatment effects on lipid metabolism favored the efavirenz + emtricitabine + tenofovir DF regimen.