



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:	Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate
Doses and Formulations:	EFV 600 mg QD, FTC 200 mg QD, and TDF 300 mg QD or EFV 600 mg QD and FTC/TDF 200 mg/300 mg QD
Indication:	HIV-1 Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, California 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 Subject Screened)
Study End Date:	17 January 2007 (Last Subject Observation for Week 144 Analysis, Study Ongoing)
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Report Date:	02 May 2007
Synopsis Date:	25 March 2008
Previous Report Dates:	27 June 2006 (Week 96 Interim Clinical Study Synopsis) 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, California 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 the European Union screened at least one subject

Publications:

Enejosa J, Chen SS, Cheng AK. Efficacy and safety of tenofovir DF (TDF)-containing versus thymidine analog-containing regimens in antiretroviral-naive HIV-1-infected women [poster]. HIV DART 2006: Frontiers in Drug Development for Antiretroviral Therapies; 2006 December 10–14; Cancun, Mexico.

Gallant JE, Pozniak AL, Staszewski S, DeJesus E, Chen SS, Enejosa J, et al. Efficacy and safety of tenofovir DF (TDF)-containing versus non-TDF-containing regimens in black antiretroviral-naive patients [poster number 505]. 14th Conference on Retroviruses and Opportunistic Infections; 2007 February 25–28; Los Angeles, Calif, USA.

Pozniak AL, Gallant JE, DeJesus E, Arribas JR, Campo RE, Chen S-S, et al. Efficacy and safety of tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) compared to fixed dose zidovudine/lamivudine (CBV) and EFV through 96 weeks in antiretroviral treatment-naive patients [poster number P6]. 8th International Congress on Drug Therapy in HIV Infection; 2006 November 12–16; Glasgow, UK.

McColl DJ, Margot NA, Chuang S, Chen SS, Cheng AK, Miller MD. Study 934: Lower rates of resistance development associated with tenofovir DF and emtricitabine plus efavirenz by week 96 [poster number P199]. 8th International Congress on Drug Therapy in HIV Infection; 2006 November 12–16; Glasgow, UK.

Staszewski S, Pozniak AL, Gallant JE, DeJesus E, Chen SS, Enejosa J, et al. Renal safety profile of tenofovir DF (TDF)-containing compared to non-TDF-containing regimens in antiretroviral-naive patients with mild renal impairment or hypertension and/or diabetes mellitus [poster number P157]. 8th International Congress Drug Therapy in HIV Infection; 2006 November 12–16; Glasgow, UK.

STUDY SYNOPSIS (CONTINUED)

Publications (continued):

McColl DJ, Margot NA, Chuang S, Chen SS, Cheng AK, Miller MD. Study 934: Lower rates of resistance development associated with tenofovir DF and emtricitabine plus efavirenz by week 96 [poster number H-1004]. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2006 September 27–30; San Francisco, Calif, USA.

Pozniak AL, Gallant JE, DeJesus E, Arribas JR, Gazzard B, Campo RE, et al. Tenofovir Disoproxil Fumarate, Emtricitabine, and Efavirenz Versus Fixed-Dose Zidovudine/Lamivudine and Efavirenz in Antiretroviral-Naive Patients: Virologic, Immunologic, and Morphologic Changes: A 96-Week Analysis. *JAIDS* 2006;43 (5):535-40.

Gallant JE, Pozniak AL, DeJesus E, Arribas JR, Campo R, Chen S-S, et al. Efficacy and safety of tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) compared to fixed dose zidovudine/lamivudine (CBV) and EFV through 96 weeks in antiretroviral treatment-naive patients [poster number TUPE0064]. XVI International AIDS Conference; 2006 August 13–18; Toronto, Canada.

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-naïve patients [poster number PE13.2/16]. 10th European AIDS Conference (EACS); 2005 November 17–20; Dublin, Ireland.

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-naïve patients [poster number 23]. 2nd International Workshop on HIV and Hepatitis Co-Infection; 2006 January 12–14; Amsterdam, The Netherlands.

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.

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

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-naïve HIV-infected patients: a 48-week analysis [poster number PE7.3/14]. 10th European AIDS Conference (EACS); 2005 Nov 17–20; Dublin Ireland.

STUDY SYNOPSIS (CONTINUED)

Publications (continued):

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

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 [poster WeOa0202]. 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment; 2005 July 24–27; Rio de Janeiro, Brazil.

McColl 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, 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.

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.

Study Period:

29 July 2003 (First subject screened)

17 January 2007 (Last subject observation for the Week 144 analysis; study ongoing)

Phase of Development: Phase 3

STUDY SYNOPSIS (CONTINUED)

Objectives:

The primary objective of this study, which was addressed in the Week 48 interim clinical study report (29 April 2005), was as follows:

- To assess noninferiority of tenofovir disoproxil fumarate (tenofovir DF, TDF) and emtricitabine (FTC) in combination with efavirenz (EFV) relative to Combivir in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive subjects, as determined by the achievement and maintenance of confirmed HIV-1 RNA < 400 copies/mL through Week 48, 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 that were addressed in the Week 48 interim clinical study report (29 April 2005) or the Week 96 interim clinical study synopsis (27 June 2006) were as follows:

- To assess noninferiority of tenofovir DF and emtricitabine in combination with efavirenz relative to Combivir in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive subjects, as determined by the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Week 48, defined by the FDA TLOVR algorithm
- To assess noninferiority of tenofovir DF and emtricitabine in combination with efavirenz relative to Combivir in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive subjects, as determined by the achievement and maintenance of confirmed HIV-1 RNA < 400 copies/mL and < 50 copies/mL through Week 96, defined by the FDA TLOVR algorithm

The secondary objectives of this study that are addressed in this Week 144 interim clinical study report were as follows:

- To evaluate the safety and tolerability of the two treatment regimens in subjects through 144 weeks of drug exposure
- To assess noninferiority of tenofovir DF and emtricitabine in combination with efavirenz relative to Combivir in combination with efavirenz in the treatment of HIV-1 infected antiretroviral-naive subjects, as determined by the achievement and maintenance of confirmed HIV-1 RNA < 400 copies/mL and < 50 copies/mL through Week 144, defined by the FDA TLOVR algorithm
- To assess the incidence of hyperpigmentation in both treatment groups
- To evaluate the effect of dosing tenofovir DF and emtricitabine without regard to meals

STUDY SYNOPSIS (CONTINUED)

Objectives (continued):

The following secondary study objectives are not addressed in this interim clinical study report because they are not applicable for the Week 144 time point:

- To evaluate the long-term efficacy, safety, tolerability of treatment with emtricitabine, tenofovir DF, and efavirenz through 240 weeks of drug exposure
- To evaluate the safety, tolerability, efficacy, and benefits of switching from a Combivir (twice daily) and efavirenz (once daily) regimen to a fixed-dose, triple combination formulation regimen of efavirenz/emtricitabine/tenofovir DF (once daily)

Methodology: The first 144 weeks of this study were of a randomized, open-label, parallel, multicenter, active-controlled design to assess the noninferiority of two treatment regimens: efavirenz + emtricitabine + tenofovir DF (i.e., the emtricitabine + tenofovir DF group) versus efavirenz + Combivir (i.e., the Combivir group). Approximately 500 subjects meeting inclusion and exclusion criteria were to be enrolled in the study. Subjects were randomized in a 1:1 ratio to the emtricitabine + tenofovir DF group, which received emtricitabine 200 mg and tenofovir DF 300 mg, each once daily, or the Combivir group, which received Combivir (lamivudine/zidovudine, 150 mg/300 mg) twice daily. All subjects also received efavirenz 600 mg once daily. Subjects were stratified on the basis of screening CD4+ cell count (< or \geq 200 cells/mm³).

The regimen of efavirenz + emtricitabine + tenofovir DF was administered as the individual products for the first 96 weeks and, subsequently, as efavirenz plus the fixed-dose combination of emtricitabine/tenofovir DF through 144 weeks.

Physical examinations and laboratory examinations were conducted at screening, prebaseline, baseline, Week 2, Week 4, Week 8, every 8 weeks through Week 48, every 12 weeks from Weeks 48 through 144, and within 30 days after early study discontinuation or study completion. Whole-body dual-energy x-ray absorptiometry (DEXA) scans were performed at Week 48 at selected sites (i.e., sites whose DEXA facilities had previously performed whole-body DEXA scans and were certified by the Gilead-selected DEXA vendor) and at Weeks 96 and 144 for all subjects continuing in the study.

After completing 144 weeks of treatment with study drugs, subjects from both study groups were 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 (EFV/FTC/TDF).

This interim clinical study report presents data for each subject up to the switch to the EFV/FTC/TDF fixed-dose, triple-combination formulation.

STUDY SYNOPSIS (CONTINUED)

Number of Subjects (Planned and Analyzed):

Planned: 500 (250 subjects in each treatment group)

Randomized: 517

Analyzed: 511 (257 subjects in the tenofovir DF + emtricitabine group and 254 subjects in the Combivir group)

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

Duration of Treatment: 240 weeks

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, ETA038A, ERF412A-A, ETA049A, and ETF340A), 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, J206B2, J206B2-A, J305B1, and J305B1-B); emtricitabine/tenofovir DF 200 mg/300 mg once daily orally, with out regard to meals (Lot Nos. V305B1, V305B1-A, V402B1, and V406B1); nevirapine 200 mg twice daily orally (according to the nevirapine prescribing information found in 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, 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, R166903, 5ZP6086, and R217396); nevirapine 200 mg twice daily orally (according to the nevirapine prescribing information found in the protocol) could replace efavirenz in the event of efavirenz-associated CNS toxicity

Criteria for Evaluation for the Week 144 Interim Analysis:

Efficacy: Achievement and maintenance of confirmed HIV-1 RNA < 400 copies/mL and < 50 copies/mL through Week 144, as defined by the FDA TLOVR algorithm; time to loss of virologic response; time to pure virologic failure; change from baseline in HIV-1 RNA and CD4+ cell count

Safety: Adverse events, clinical laboratory tests, body morphology/fat distribution (based on whole-body DEXA scans)

STUDY SYNOPSIS (CONTINUED)

Statistical Methods:

The primary safety and efficacy analysis, conducted upon completion of 48 weeks on study by the last enrolled subject, was presented in the Week 48 interim clinical study report (29 April 2005). Additionally, results of secondary analyses at Weeks 48 and 96 were presented in the Week 48 interim clinical study report and the Week 96 interim clinical study synopsis (26 June 2006), respectively, and are not described in detail in this report.

This Week 144 interim clinical study report presents safety and efficacy analyses of all data collected while subjects were receiving randomized study regimen; data collected after subjects rolled over into the extension phase and received the EFV/FTC/TDF fixed-dose, triple combination tablet were excluded.

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 (described in the Week 48 interim clinical study report).

For the TLOVR outcomes analyses and responder analyses at Week 144, the efficacy analysis set excluded the following subjects from the modified intent-to-treat (MITT) analysis set: (a) all Week 48 responders who did not consent to continue in the study after Week 48 and (b) all Week 96 responders who did not consent to continue in the study after Week 96. The noninferiority of the efavirenz + emtricitabine + tenofovir DF regimen relative to the efavirenz + Combivir regimen through 144 weeks was assessed using a two-sided 95% confidence interval (CI) for the baseline CD4+ cell count stratum-weighted difference in the proportions of subjects who achieved and maintained confirmed HIV-1 RNA < 400 copies/mL and < 50 copies/mL at Week 144 (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 144 interim analysis included treatment-emergent adverse events, deaths and serious adverse events, adverse events leading to discontinuation of study drug, clinical laboratory toxicities, and body morphology/fat distribution (based on whole-body DEXA scans). Adverse events and serious adverse events are summarized by system organ class, high level term, and preferred term (from the Medical Dictionary for Regulatory Activities) and presented by treatment group; deaths are listed by subject. Descriptive statistics of baseline values and change from baseline for protocol-specified clinical laboratory analytes and the number and percentage of subjects with laboratory abnormalities are provided. Summaries of body composition in limb fat, trunk fat, and total body fat by study visit are presented by treatment.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS:

Efficacy Results—Week 144: The results of the secondary efficacy analysis at Week 144 demonstrated continued significant and potent antiretroviral efficacy of the once-daily regimen of efavirenz + emtricitabine + tenofovir DF through 144 weeks of treatment.

A significantly higher proportion of subjects in the emtricitabine + tenofovir DF group (71%, 161/227) compared with the Combivir group (58%, 133/229) achieved and maintained plasma HIV-1 RNA < 400 copies/mL through Week 144, as defined by the TLOVR algorithm (i.e., were Week 144 responders for HIV-1 RNA < 400 copies/mL; $p = 0.004$; 95% CI, 4% to 22%). Because the lower bound of the 95% confidence interval for the treatment effect lies above the limit of ≥ -0.13 required for demonstration of noninferiority and, furthermore, the 95% confidence interval 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.

Similarly, the proportion of Week 144 responders (HIV-1 RNA < 50 copies/mL) was higher for the emtricitabine + tenofovir DF group (64%, 146/227) compared with the Combivir group (56%, 130/231), although the difference was not statistically significant ($p = 0.082$).

STUDY SYNOPSIS (CONTINUED)

Efficacy Results—Week 144 (continued): The superiority of the efavirenz + emtricitabine + tenofovir DF regimen compared with the efavirenz + Combivir regimen is further supported by analysis of the time to loss of virologic response. The Kaplan-Meier estimate for the proportion of subjects with loss of virologic response (HIV-1 RNA cutoff value of 400 copies/mL) by Week 144 was significantly lower for the emtricitabine + tenofovir DF group compared with the Combivir group (28% vs. 41%, overall $p = 0.003$). Similarly, when the cutoff value for HIV-1 RNA was 50 copies/mL, the Kaplan-Meier estimate for the proportion of subjects with loss of virologic response by Week 144 was also lower for emtricitabine + tenofovir DF group compared with the Combivir group (34% vs. 43%), although the difference was not statistically significant. The Kaplan-Meier estimate for the proportion of subjects with pure virologic failure also was lower for the emtricitabine + tenofovir DF group compared with the Combivir group when the cutoff value for HIV-1 RNA was 400 copies/mL (11% vs. 17%) or 50 copies/mL (21% vs. 25%), although the difference was not statistically significant.

Mean decreases in plasma HIV-1 RNA from baseline to Week 144 were similar between the two treatment groups (3.32 \log_{10} copies/mL for the emtricitabine + tenofovir DF group and 3.30 \log_{10} copies/mL for the Combivir group).

Mean increases in CD4+ cell count from baseline to Week 144 were greater for the emtricitabine + tenofovir DF group than for the Combivir group (312 vs. 271 cells/mm³), although the difference was not statistically significant.

Within subgroups based on baseline plasma HIV-1 RNA (> 100,000 copies/mL or $\leq 100,000$ copies/mL), the proportion of Week 144 responders (HIV-1 RNA < 400 copies/mL) was higher in the emtricitabine + tenofovir DF group than in the Combivir group, and the difference was significant for subjects with baseline plasma HIV-1 RNA > 100,000 copies/mL (73% vs. 59%, respectively; $p = 0.020$). Similarly, the proportion of Week 144 responders (HIV-1 RNA < 50 copies/mL) favored the emtricitabine + tenofovir DF group; however, statistical significance was not attained.

Within subgroups based on baseline CD4+ cell counts (≥ 200 cells/mm³ or < 200 cells/mm³ and ≥ 50 cells/mm³ or < 50 cells/mm³), the proportion of Week 144 responders (HIV-1 RNA < 400 copies/mL) was higher in the emtricitabine + tenofovir DF group than in the Combivir group, and the difference was significant for subjects with baseline CD4+ cell counts ≥ 200 cells/mm³ (72% vs. 57%, respectively; $p = 0.013$) and subjects with baseline CD4+ cell counts ≥ 50 cells/mm³ (71% vs. 59%, $p = 0.008$). Similarly, the proportion of Week 144 responders (HIV-1 RNA < 50 copies/mL) was higher in the emtricitabine + tenofovir DF group than in the Combivir group, and the difference was statistically significant for subjects with baseline CD4+ cell counts ≥ 200 cells/mm³ (69% vs. 57%, respectively; $p = 0.050$).

STUDY SYNOPSIS (CONTINUED)

Efficacy Results—Week 144 (continued): New (postbaseline) presumed or confirmed CDC Category C AIDS-defining events were reported for 13 subjects (nine in the emtricitabine + tenofovir DF group and four in the Combivir group). All reported new Category C events had an onset date before Week 48.

Resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed in both treatment groups (5% [13/244] in the emtricitabine + tenofovir DF group and 9% [21/243] in the Combivir group). The M184V/I mutation, selected by emtricitabine or lamivudine, developed significantly less frequently in the emtricitabine + tenofovir DF group (1%, 2/244) compared with the Combivir group (4%, 10/243, $p = 0.021$). Two subjects in the Combivir group developed thymidine analog mutations, specifically, D67N or K70R mutations in the reverse transcriptase gene. Through Week 144, no subject developed the K65R mutation that can be selected by tenofovir.

Through 144 weeks of treatment, during which study drugs were administered without regard to food, the proportions of Week 144 responders (HIV-1 RNA < 400 copies/mL) among subjects who responded to the dosing questionnaire were similar between those who reported routinely dosing the regimen of efavirenz + emtricitabine + 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 (98% vs. 94%, respectively; $p = 0.68$, Fisher exact test). Similarly, 90% of subjects who reported dosing with food compared with 86% of subjects who reported dosing without food were Week 144 responders (HIV-1 RNA < 50 copies/mL).

STUDY SYNOPSIS (CONTINUED)

Safety Results: Through Week 144, the overall incidence of treatment-emergent adverse events (AEs) was similar between the two treatment groups. Treatment-emergent AEs were reported for 95% of subjects (245/257) in the emtricitabine + tenofovir DF group and 97% of subjects (246/254) in the Combivir group. The most frequently reported treatment-emergent AEs (for at least 20% of either treatment group) were diarrhea (28%, 73/257), dizziness (28%, 71/257), nausea (26%, 66/257), and headache (20%, 51/257) in the emtricitabine + tenofovir DF group and nausea (33%, 83/254), dizziness (29%, 74/254), and diarrhea (20%, 50/254) in the Combivir group. Grade 3 or 4 treatment-emergent AEs were reported for 21% of subjects (53/257) in the emtricitabine + tenofovir DF group and 23% of subjects (59/254) in the Combivir group. The only Grade 3 or 4 AEs reported for more than 1% of subjects in either treatment group were anemia, reported for no subject in the emtricitabine + tenofovir DF group and 10 subjects (4%) in the Combivir group, and diarrhea, reported for four subjects (2%) in the emtricitabine + tenofovir DF group and one subject (< 1%) in the Combivir group. Treatment-emergent AEs generally were reported with similar frequency among all subgroups (sex, age, race) for both treatment groups.

Treatment-emergent AEs considered by the investigator as possibly or probably related to study drugs (emtricitabine + tenofovir DF or Combivir) were reported for 33% of subjects (86/257) in the emtricitabine + tenofovir DF group and 51% of subjects (130/254) in the Combivir group. In both treatment groups, the most frequently reported treatment-emergent AE (for at least 10% of either treatment group) related to study drugs was nausea (12% [32/257] in the emtricitabine + tenofovir DF group and 26% [65/254] in the Combivir group). Of the Grade 3 or 4 AEs considered by the investigator as possibly or probably related to study drugs, only anemia (reported in 0% of subjects in the emtricitabine + tenofovir DF group and 4% of subjects [10/254] in the Combivir group) and neutropenia (reported in < 1% of subjects [1/257] in the emtricitabine + tenofovir DF group and 1% of subjects [3/254] in the Combivir group) were reported in more than one subject in either treatment group.

Treatment-emergent AEs considered by the investigator as possibly or probably related to the complete study regimen (efavirenz + emtricitabine + tenofovir DF or efavirenz + Combivir) were reported for 69% of subjects (177/257) in the emtricitabine + tenofovir DF group and 76% of subjects (193/254) in the Combivir group. The most frequently reported treatment-emergent AEs (for at least 10% of either treatment group) related to study regimen were dizziness (25%, 63/257), nausea (18%, 46/257), and abnormal dreams (17%, 44/257) in the emtricitabine + tenofovir DF group and nausea (27%, 69/254), dizziness (26%, 66/254), abnormal dreams (13%, 34/254), and fatigue (10%, 25/254) in the Combivir group.

STUDY SYNOPSIS (CONTINUED)

Safety Results (continued): Five deaths (two in the emtricitabine + tenofovir DF group and three in the Combivir group) have occurred in this study. Of the two subjects 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 three subjects in the Combivir group, one died of progressive multifocal leukoencephalopathy due to acquired immunodeficiency syndrome (AIDS), one died because of a suspected heroin overdose, and one died because of metastatic carcinoma (the primary site was unknown). All deaths were assessed by the investigator as not related to study regimen.

The overall incidence of treatment-emergent serious adverse events (SAEs) was similar between the two treatment groups (11% in the emtricitabine + tenofovir DF group and 14% in the Combivir group). Anemia (no subjects in the emtricitabine + tenofovir DF group and 3% of subjects in the Combivir group) was the only SAE considered by the investigator as possibly or probably related to study drugs.

Adverse events leading to study drug discontinuation occurred in a significantly smaller percentage of subjects in the emtricitabine + tenofovir DF group compared with the Combivir group (5% vs. 11%, $p = 0.010$). The most frequently occurring AE leading to study drug discontinuation was anemia, including decreased hemoglobin (no subjects in the emtricitabine + tenofovir DF group and 6% of subjects in the Combivir group).

The incidence of bone fractures was lower in the emtricitabine + tenofovir DF group (six events) than in the Combivir group (eight 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.

Analysis of renal clinical laboratory parameters indicated a small but statistically significant decrease from baseline to Week 144 in estimated glomerular filtration rate for the emtricitabine + tenofovir DF group. However, the significance of this change is unknown, particularly because there were no study drug discontinuations due to renal AEs, no reports of Fanconi syndrome or tubulopathy, no confirmed reports of Grade 3 or 4 serum creatinine elevation, and no reports of Grade 3 or 4 serum phosphorus decrease.

STUDY SYNOPSIS (CONTINUED)

Safety Results (continued): Incidences of skin hyperpigmentation were generally mild in severity. Adverse events of skin hyperpigmentation were reported for 24 subjects (15 in the emtricitabine + tenofovir DF group and nine in the Combivir group). For nine of the 24 subjects (eight in the emtricitabine + tenofovir DF group and one in the Combivir group), the hyperpigmentation was assessed by a dermatologist as not related to study drugs. In the remaining 15 subjects, hyperpigmentation was assessed by a dermatologist as related or probably related to study drugs for 11 subjects (six in the emtricitabine + tenofovir DF group and five in the Combivir group), was pending dermatologist assessment for one subject, and was not assessable for three subjects because they refused dermatologist evaluation. The hyperpigmentation was Grade 2 in severity for two subjects (one in each treatment group) and Grade 1 for all other subjects.

The mean increases in fasting serum triglyceride and total cholesterol concentrations from baseline to Week 144 were significantly smaller for the emtricitabine + tenofovir DF group relative to the Combivir group (3.64 mg/dL vs. 35.50 mg/dL, respectively, and $p = 0.047$ for triglycerides; 24.08 mg/dL vs. 35.67 mg/dL, respectively, and $p = 0.005$ for total cholesterol).

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 kg vs. 6.92 kg, respectively; $p = 0.035$) and at Week 144 (9.22 kg vs. 6.50 kg, respectively; $p < 0.001$). From Week 48 to Week 144, the mean body composition in limb fat increased significantly for the emtricitabine + tenofovir DF group (+1.13 kg, $p < 0.001$), but decreased significantly for the Combivir group (-1.09 kg, $p < 0.001$); the difference between the two treatment groups was significant ($p < 0.001$).

The mean body composition in trunk fat at Week 48 and Week 144 was greater in the emtricitabine + tenofovir DF group than the Combivir group, but the differences were not significant. From Week 48 to Week 144, the mean body composition in trunk fat increased significantly for the emtricitabine + tenofovir DF group (+1.30 kg, $p = 0.001$), and decreased slightly in the Combivir group (-0.10 kg); the difference between the two treatment groups was significant ($p < 0.011$).

The mean body composition in total body fat was greater in the emtricitabine + tenofovir DF group compared with the Combivir group at Week 48 (20.58 kg vs. 16.98 kg, respectively) and Week 144 (21.73 kg vs. 17.50 kg, respectively), and the difference was statistically significant at Week 144 ($p = 0.001$). From Week 48 to Week 144, the mean body composition in total body fat increased significantly for the emtricitabine + tenofovir DF group (+2.47 kg, $p < 0.001$), but decreased for the Combivir group (-1.18 kg); the difference between the two treatment groups was significant ($p < 0.001$).

STUDY SYNOPSIS (CONTINUED)

Safety Results (continued): Seven pregnancies have been reported in this study, four in the emtricitabine + tenofovir DF group and three in the Combivir group. All reported pregnancies occurred during the first 48 weeks of the study. The outcome of one pregnancy is unknown. Of the six pregnancies for which outcomes are known, one pregnancy (emtricitabine + tenofovir DF group) was ectopic, two pregnancies (one in the Combivir group, one in the emtricitabine + tenofovir DF group) ended by therapeutic abortion, one pregnancy (Combivir group) ended with spontaneous abortion, and two pregnancies (both in the emtricitabine + tenofovir DF group) each resulted in liveborn delivery of one infant with no congenital abnormalities.

CONCLUSIONS:

- In antiretroviral treatment-naive HIV-1 infected subjects, the once-daily regimen of efavirenz + emtricitabine + tenofovir DF administered without regard to food demonstrated potent and durable antiviral efficacy through 144 weeks of treatment. Through 144 weeks, the regimen of efavirenz + emtricitabine + tenofovir DF was superior to the regimen of efavirenz + Combivir for achievement and maintenance of plasma HIV-1 RNA concentrations < 400 copies/mL. Immunologic benefit continued, as evidenced by increases from baseline in mean CD4+ cell count.
- Through 144 weeks, resistance to efavirenz was the most common form of resistance to develop. Resistance to emtricitabine (M184V/I mutation, which also is selected for by lamivudine) developed infrequently, and no resistance to tenofovir DF (K65R mutation) developed through Week 144.
- Treatment response rates were similar among subjects who dosed their study regimen with food and those who dosed without food.
- The once-daily regimen of efavirenz + emtricitabine + tenofovir DF continued to be well tolerated through 144 weeks and demonstrated a preferential safety profile compared with the efavirenz + Combivir regimen, as evidenced by the significantly lower rate of study drug discontinuation due to an adverse event.
- In the emtricitabine + tenofovir DF group, a small decrease from baseline in estimated glomerular filtration rate was observed; the significance of this change is unknown, particularly because no subject discontinued study drugs because of a renal adverse event, no Fanconi syndrome or tubulopathy was reported, no confirmed Grade 3 or 4 serum creatinine elevation was reported, and no subject experienced a Grade 3 or 4 serum phosphorus decrease.
- The rate of treatment-related hyperpigmentation was similar between both treatment groups.