



## FINAL CLINICAL STUDY REPORT

---

**Study Title:** Phase IV, Open-label, Randomized, Multicenter Study Evaluating Efficacy and Tolerability of Single Tablet Regimen of Efavirenz/Emtricitabine/Tenofovir DF Compared to Unmodified HAART in HIV-1 Infected Subjects Who Have Achieved Virological Suppression on their HAART Regimen

**Name of Test Drug:** Efavirenz/Emtricitabine/Tenofovir DF (Atripla<sup>®</sup>)

**Dose and Formulation:** Tablet containing efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg

**Indication:** Human immunodeficiency virus infection

**Sponsor:** Bristol-Myers Squibb & Gilead Sciences, LLC  
777 Scudders Mill Road  
Plainsboro, NJ 08536

**Study No.:** AI266073 (GS-US-177-0107)

**Phase of Development:** Phase 4

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

**Study Start Date:** 28JUL2006 (First Subject Screened)  
**Study End Date:** 18OCT2007 (Last Subject Observation)

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

**Responsible Medical Monitor:** Name: Cindy Elko-Simms, MD  
Telephone: +1 (888) 483-7729  
Fax: +1 (888) 529-3580

**Report Date:** 11MAR2008

---

### CONFIDENTIAL AND PROPRIETARY INFORMATION

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

## STUDY SYNOPSIS

**Bristol-Myers Squibb & Gilead Sciences, LLC**  
**777 Scudders Mill Road**  
**Plainsboro, NJ 08536**  
**United States of America**

---

<b>Title of Study:</b> Phase IV, Open-label, Randomized, Multicenter Study Evaluating Efficacy and Tolerability of Single Tablet Regimen of Efavirenz/Emtricitabine/Tenofovir DF Compared to Unmodified HAART in HIV-1 Infected Subjects Who Have Achieved Virological Suppression on their HAART Regimen
<b>Investigators:</b> Multicenter
<b>Study Centers:</b> Subjects were randomized at 53 sites in the United States and 2 sites in Puerto Rico
<b>Publications:</b> DeJesus E, Young B, Fisher A, Ebrahimi R, Maa J-F, Seekins D, et al. Virologic suppression is maintained after change of efavirenz/emtricitabine/tenofovir disoproxil fumarate single tablet regimen (EFV/FTC/TDF) vs. continuation of current antiretroviral therapy: Study 073 – Results of 24-week interim efficacy analyses [presentation LBPS7/6]. 11th European AIDS Conference; 2007 October 26; Madrid, Spain.
<b>Study Period:</b> 28JUL2006 (First subject screened) 18OCT2007 (Last subject observation)
<b>Phase of Development:</b> 4

**Objectives:**

The primary objective of this study was as follows:

- To compare the effectiveness (efficacy, safety, and tolerability) in subjects on a single-tablet regimen to that of subjects continuing unmodified highly active antiretroviral therapy (HAART) as measured by the proportion of subjects who maintain human immunodeficiency virus type 1 (HIV-1) ribonucleic acid (RNA) < 200 copies/mL on their original assigned regimen at Week 48 using the time to loss-of-virologic response (TLOVR) analysis.

The secondary objectives of this study were as follows:

- To assess the proportion of subjects with HIV-1 RNA < 200 copies/mL at Week 24.
- To assess the proportions of subjects enrolled in the study with baseline HIV-1 RNA between 50 and 200 copies/mL and HIV-1 RNA < 50 copies/mL at Weeks 24 and 48.
- To assess the proportions of subjects with HIV-1 RNA of < 50 copies/mL at Weeks 24 and 48.
- To assess the change from baseline in absolute CD4 cell count, hemoglobin, and lipid profile through Weeks 24 and 48 for each treatment group.
- To describe the safety and tolerability of each treatment group.
- To assess viral genotypic analysis at time of virologic rebound.
- To assess the change in HIV symptom index for each treatment group.
- To assess the change from baseline in quality of life within each treatment group and between treatment groups.
- To assess the change in treatment adherence from baseline within each treatment group and between treatment groups.

**Methodology:** This was a 48-week multicenter, open-label, randomized study investigating a simplification strategy that used a single-tablet regimen (Atripla) in HIV-1 infected subjects whose viral loads were suppressed on their current unmodified HAART regimen.

Three hundred subjects were equally stratified by the use of protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) in the treatment regimen at study entry. Each stratum was to enroll subjects who were randomly assigned in a 2:1 ratio to group 1 (switch to the single-tablet regimen of Atripla) or Group 2 (stay on their baseline regimen [SBR], i.e., continuing with their current HAART).

**Number of Subjects (Planned and Analyzed):**

Planned: 296  
Analyzed: Randomized 306  
Treated 300 (included in both intent-to-treat [ITT] and safety analysis sets)

**Diagnosis and Main Criteria for Inclusion:** Male and nonpregnant female ( $\geq 18$  years old), virologically suppressed ( $\geq 3$  months), HIV-1 infected subjects with a confirmed HIV-1 RNA concentration of < 200 copies/mL. All subjects had to have adequate renal function (creatinine clearance  $\geq 60$  mL/min according to Cockcroft-Gault formula).

**Duration of Treatment:** 48 weeks

**Test Product, Dose, Mode of Administration, and Batch No.:** Fixed-dose combination tablet containing 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate (tenofovir DF), administered orally as one tablet, once daily, on an empty stomach preferably at bedtime. Batch numbers: AA512B2 and AA0601B3

**Reference Therapy, Dose, Mode of Administration, and Batch No.:** Subjects in the SBR group continued unmodified HAART.

**Criteria for Evaluation:**

**Efficacy:** Efficacy was assessed by regular monitoring of HIV-1 RNA concentrations and CD4 cell count.

**Safety:** Safety was assessed by recording adverse events (AEs), clinical laboratory evaluations, vital signs, body weight, and physical examination findings.

**Outcomes Research:** Outcomes research assessments included quality of life (Short Form-36 [SF-36] Version 2), adherence by visual analog scale (VAS), Preference of Medication (POM) questionnaire (Atripla group only), Perceived Ease of Regimen for Condition (PERC) survey, and an HIV symptom index questionnaire.

**Statistical Methods:**

**Efficacy:** The primary efficacy endpoint was the maintenance of confirmed HIV-1 RNA < 200 copies/mL, defined as the proportion of subjects with HIV-1 RNA < 200 copies/mL on their original assigned regimen at Week 48 based on TLOVR analysis. The primary analysis of the primary efficacy endpoint was in the ITT analysis set, and assumed noncompleters = failure. Noncompleters were subjects who prematurely discontinued in the study for any reason. Responders were subjects who maintained HIV-1 RNA < 200 copies/mL without confirmed virologic rebound up to Week 48. Confirmed virologic rebound was defined as on-study HIV-1 RNA  $\geq$  200 copies/mL on two successive occasions or last on-study HIV-1 RNA  $\geq$  200 copies/mL followed by discontinuation. The Atripla group was to be declared noninferior to the SBR group if the lower confidence boundary of the responder difference (Atripla minus SBR) was greater than -0.15. TLOVR responder analysis for HIV-1 RNA < 50 copies/mL was performed in a similar manner to the analysis described for the primary endpoint analysis.

Pure virologic response (PVR) for HIV-1 RNA < 50, < 200, and < 400 copies/mL occurred if the subjects had no confirmed rebound to  $\geq$  threshold or last observation  $\geq$  threshold followed by study discontinuation through Week 24 or Week 48. The PVR rate was the proportion of subjects who did not have a pure virologic failure (PVF) at the specified timepoint. PVF was estimated using the Kaplan-Meier (KM) product limit method. Time to PVF was the time to the earliest date of confirmed HIV-1 RNA above threshold (two consecutive HIV-1 RNA  $\geq$  threshold, or the last HIV-1 RNA  $\geq$  threshold) up to the end of the visit window for the specified time point of analysis (e.g., Day 210 for analysis of PVR at Week 24).

**Statistical Methods:**

**Efficacy (cont):** A post-hoc sensitivity analysis of the PVR endpoint for HIV-1 RNA < 50 copies/mL was conducted to minimize the effect of censoring in the Week 48 window. The time of all censored observations in the Week 48 visit window was reset to 1 day after the last observed event in the study. This approach was considered since the KM estimate was greatly affected by heavy censoring occurring prior to a few events in the Week 48 window (two subjects in each group had unconfirmed HIV-1 RNA > 50 copies/mL at the end of the study and were considered failures; there were no failures at the HIV-1 RNA thresholds of < 200 or < 400 copies/mL in the Week 48 visit window).

The proportion of subjects with HIV-1 RNA < threshold at each visit was based on the number of subjects with HIV-1 RNA < threshold (< 50, < 200, and < 400 copies/mL) at each visit divided by the number of study subjects. Analyses were performed in which subjects with missing HIV-1 RNA levels were analyzed as failures (M = F), in which subjects with missing HIV-1 RNA values were excluded (M = E), and in which the last observation was carried forward (LOCF). The differences in percentages between treatment groups and stratum adjusted two-sided 95% CI (as calculated for the primary endpoint) for the difference in percentages for Week 24 and Week 48 are presented.

CD4 absolute values and change from baseline in CD4 by each visit and for the last observed value were summarized by treatment group and overall. Changes from baseline for CD4 by each visit within each treatment group are compared using the Wilcoxon signed rank test; changes from baseline between treatment groups are compared using the Wilcoxon rank sum test.

**Safety:** Safety assessments were summarized using descriptive statistics, with changes from baseline and statistical tests when appropriate. Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA<sup>®</sup>), Version 10. All safety data were listed.

**Outcomes Research:** Outcomes measures were summarized using descriptive statistics. Changes from baseline within and between treatment groups were analyzed using appropriate statistical tests. Dichotomized responses are presented and analyzed for PERC survey results (very easy versus not very easy) and HIV symptom index scores (no symptom versus with symptom).

## **SUMMARY – RESULTS:**

**Efficacy Results:** High rates of virologic suppression were maintained in virologically suppressed subjects who switched therapy to Atripla or stayed on their baseline regimen. The primary analysis of the primary endpoint (HIV-1 RNA < 200 copies/mL, ITT analysis set, noncompleters = failure) demonstrated that the proportion of responders, as defined by the TLOVR algorithm, was similar in the two treatment groups at Week 48 (89% Atripla and 88% SBR, difference between groups for Atripla minus SBR 1.1%, 95% CI –6.7% to 8.8%,  $p = 0.82$ ). Since the lower confidence boundary for the responder difference (Atripla minus SBR) was greater than –15%, the Atripla group is declared noninferior to the SBR group.

The sensitivity analysis using all randomized subjects (HIV-1 RNA < 200 copies/mL, noncompleters and subjects who did not receive study drug were treated as failures) also demonstrated noninferiority for Atripla versus SBR for the proportion of responders, as defined by the TLOVR algorithm at Week 48 (89% Atripla and 83% SBR; difference between groups for Atripla minus SBR 5.4%, 95% CI –3.1% to 13.8%,  $p = 0.53$ ).

For the viral load threshold of < 50 copies/mL (ITT analysis set, noncompleters = failure), the proportion of responders as defined by the TLOVR algorithm was similar in the two treatment groups at Week 48 (87% Atripla and 85% SBR; difference between groups for Atripla minus SBR 2.6%, 95% CI –5.9% to 11.1%,  $p = 0.54$ ).

PVR rates were high in both treatment groups throughout the study for thresholds of HIV-1 RNA < 50, < 200, or < 400 copies/mL. The overall PVR rate for HIV-1 RNA < 50 copies/mL was similar in the two treatment groups through Week 48 (95% for Atripla and 86% for SBR; difference between groups 8.9%, 95% CI –7.7% to 25.6%), and was also very similar for thresholds of < 200 copies/mL (98% for Atripla and 99% for SBR) and < 400 copies/mL (100% in both groups). The overall PVR rate for HIV-1 RNA < 50 copies/mL remained similar in the two treatment groups through Week 48 in the sensitivity analysis to minimize the effect of censored observations (success cases) (95% Atripla and 96% SBR, difference between groups for Atripla minus SBR –0.2%, 95% CI –5.3% to 5.0%). Similarity in PVR rates for HIV-1 RNA < 50, < 200, or < 400 copies/mL between treatments was also observed within subgroups (prior PI- or NNRTI-based regimens, and whether subjects had or had not received a tenofovir DF-based regimen).

The proportions of subjects with HIV-1 RNA < 50, < 200, and < 400 copies/mL were high in both treatment groups throughout the study, and overall, no clinically relevant differences between treatment groups were seen. At Week 48 (M = F method), 88% of subjects in each treatment group had HIV-1 RNA < 50 copies/mL; 89% of subjects in the Atripla group and 90% of subjects in the SBR group had HIV-1 RNA < 200 copies/mL and < 400 copies/mL.

Subjects had high CD4 cell counts at baseline (medians: Atripla 517 cells/ $\mu$ L, SBR 515 cells/ $\mu$ L), and no clinically relevant changes in CD4 and CD8 cell counts were seen within or between treatment groups during the study.

One percent of subjects in each treatment group experienced virologic rebound in the study (defined as confirmed [two consecutive] HIV-1 RNA values  $\geq 200$  copies/mL; two subjects in the Atripla group and one subject in the SBR group).

**Efficacy Results: (cont.)** Genotyping at RT and protease was performed using standard procedures for four subjects with > 200 copies/mL of HIV-1 RNA, either due to confirmed rebound or at the last timepoint on study. Genotyping was successful on three subjects, all from the Atripla group, and failed on one subject in the SBR group due to technical reasons. One subject had a wild-type viral genotype at early termination. One subject developed resistance to efavirenz (K103N mutation) at the virologic confirmation timepoint. One subject had a complex genotype detected in the early termination sample, including M184V and a multi-nucleoside reverse transcriptase inhibitor (NRTI) resistance pattern (A62V, V75I, F77L, F116Y, and Q151M mutations), and efavirenz resistance mutations (K101E, Y188L). Secondary PI resistance mutations were also detected in this subject. As neither tenofovir DF nor emtricitabine have been shown to select for the Q151M multi-NRTI resistance pattern in vitro or in vivo, its presence in this subject may represent transmission of a resistant virus which was suppressed by the subject's regimen prior to the switch to Atripla. Therefore, only one subject had conclusive evidence of development of resistance while on Atripla, specifically the K103N efavirenz resistance mutation.

**Safety Results:** Atripla and other HAART regimens were generally well tolerated in this study. There were no deaths during the study, and treatment-emergent serious AEs (SAEs) were reported for similar proportions of subjects in the two treatment groups (6% in each group). Treatment-emergent AEs (TEAEs) that led to study drug discontinuation were experienced by 5% of subjects in the Atripla group (10 subjects) and 1% of subjects in the SBR group; the majority of subjects who discontinued study drug due to AEs had switched to Atripla from a prior PI-based regimen (seven subjects).

Similar proportions of subjects in each treatment group reported at least one TEAE in this study (81% [164 subjects] and 82% [80 subjects] in the Atripla and SBR groups, respectively). In both treatment groups, TEAEs were most frequently reported in the infections and infestations system organ class (SOC) (42% [85 subjects] and 43% [42 subjects] of subjects in the Atripla and SBR groups, respectively). Other SOCs in which more than 20% of subjects had TEAEs were as follows: Atripla group — psychiatric disorders (28%, 56 subjects); gastrointestinal disorders (26%, 52 subjects); and nervous system disorders (22%, 45 subjects); SBR group — respiratory, thoracic and mediastinal disorders (25%, 24 subjects); and gastrointestinal disorders (23%, 22 subjects). The most frequently reported TEAEs were as follows: Atripla group — dizziness (12%, 25 subjects), insomnia (10%, 21 subjects), and upper respiratory tract infection (10%, 20 subjects); SBR group — upper respiratory tract infection (10%, 10 subjects), cough (9%, nine subjects), and diarrhea (8%, eight subjects).

Treatment-emergent nervous system symptom (NSS), psychiatric symptom, and rash AEs were reported for higher proportions of subjects in the Atripla group compared to the SBR group (NSS: 21% for Atripla and 3% for SBR; psychiatric: 23% for Atripla and 10% for SBR; rash: 14% for Atripla and 6% for SBR). NSS and rash AEs were predominantly reported in subjects who had switched to Atripla from a PI-based regimen. Differences between treatment groups were primarily because higher proportions of subjects in the Atripla group compared to the SBR group experienced the following mild (Grade 1) AEs: abnormal dreams and dizziness; depression and insomnia; and rash.

**Safety Results: (cont.)** The majority of TEAEs reported in this study were Grade 1 (mild) or Grade 2 (moderate) in severity. Similar proportions of subjects in each treatment group had Grade 3 or 4 TEAEs reported (11% [23 subjects] and 7% [seven subjects] in the Atripla and SBR groups, respectively). However, for subjects who had received a prior PI-based regimen, Grade 3 or 4 TEAEs were reported for a higher proportion of subjects in the Atripla group compared to the SBR group (11% [12 subjects] versus zero subjects, respectively).

TEAEs that were considered related to study drug were reported for a higher proportion of subjects in the Atripla group compared to the SBR group (33% [67 subjects] and 5% [five subjects], respectively). In the Atripla group, the majority of subjects who experienced TEAEs considered related to study drug had switched from a PI-based regimen (49 of 67 subjects). In the Atripla group, TEAEs considered related to study drug were most frequently reported in the psychiatric disorders (16%, 33 subjects); nervous system disorders (13%, 27 subjects); and gastrointestinal disorders SOCs (7%, 15 subjects). The most frequently reported TEAE considered related to study drug were dizziness (11%, 22 subjects in the Atripla group and 1%, one subject in the SBR group) and abnormal dreams (7%, 14 subjects in the Atripla group and none in the SBR group).

There were no clinically relevant changes from baseline in mean values for hematology and chemistry parameters in either treatment group during the study (including renal parameters: serum creatinine, calculated creatinine clearance, estimated glomerular filtration rate, and serum phosphorus). Treatment-emergent laboratory abnormalities were reported for similar proportions of subjects in the two treatment groups, and overall the incidence of treatment-emergent marked laboratory abnormalities was low.

There were modest increases (improvements) in hemoglobin in the Atripla group from baseline to Weeks 24 (median increase 0.50 g/dL, 25th to 75th percentiles [Q1-Q3] 0.0 to 1.0 g/dL,  $p < 0.001$ ) and 48 (median increase 0.55 g/dL, Q1-Q3 0.0 to 1.0 g/dL,  $p < 0.001$ ); however, median values were in the normal range at baseline and throughout the study.

One HIV and hepatitis C virus coinfecting subject in the Atripla group had Grade 3 aspartate aminotransferase (AST) levels reported during the study; however, this subject had elevated AST at baseline.

Switching treatment to Atripla resulted in modest improvements in lipid parameters (fasting triglycerides and high density lipoprotein (HDL)-cholesterol), primarily the result of improvement in subjects who switched to Atripla from a prior PI-based regimen. The improvements seen were decreases from baseline to Week 48 in triglycerides (Atripla group overall  $-19.5$  mg/dL, Q1-Q3  $-54$  to  $11$  mg/dL,  $p < 0.001$ ; prior PI stratum  $-29.0$  mg/dL, Q1-Q3  $-79$  to  $0$  mg/dL,  $p < 0.001$ ), and increases from baseline in fasting HDL-cholesterol in subjects who switched to Atripla from a prior PI-based regimen ( $5.0$  mg/dL, Q1-Q3  $-2$  to  $11$  mg/dL,  $p < 0.001$ ).

There were no clinically relevant changes in median values for body weight or body mass index during the study.

**Safety Results: (cont.)** Concomitant medications were used by a lower proportion of subjects in the Atripla group (91%, 184 subjects) compared to the SBR group (98%, 95 subjects); however, these differences between groups were also present at baseline. There were notable increases from baseline in the use of lipid modifying agents in the SBR group (from 28% to 37% of subjects), and in the use of psychoanaleptics in the Atripla group (from 15% to 23% of subjects).

**Outcomes Research:** Baseline scores for quality of life (assessed using the SF-36v2) were similar to those for the general population. There were no marked changes in quality of life or treatment adherence (assessed using a VAS) for either treatment group during the study.

Subjects who received Atripla preferred it to their previous medication, as assessed using the POM survey. The proportion of subjects who considered Atripla much better than their previous regimen increased by visit, from 64% at Week 4 (116 of 182 subjects) to 85% at Week 48 (146 of 172 subjects). At Week 48, no subjects receiving Atripla considered it to be worse than their previous regimen.

HIV infected subjects in this study considered Atripla an easier regimen to follow than their previous HIV regimens, as assessed using the PERC survey. At all postbaseline assessments, differences between treatment groups were statistically significant in favour of Atripla, both overall and whether subjects had received prior NNRTI- or PI-based regimens. For all visits, significantly more subjects who received Atripla considered it an easier regimen to take than their previous regimen ( $p < 0.001$ ), whereas there were no statistically significant changes in the ease of taking the SBR regimen. At Week 48, 97% of subjects found Atripla very easy to take (172 of 178 subjects) compared to 81% of subjects in the SBR group who found their regimen easy to take (70 of 86 subjects).

Results from subject self-assessments of HIV symptoms showed long-term benefits in taking Atripla, as demonstrated by sustained reductions (improvement) in the proportions of subjects with diarrhea or loose bowel movements; bloating, pain, or gas in the stomach; changes in the way their body looked; and problems having sex. There was a transient increase (worsening) in the proportion of subjects who received Atripla and had symptoms of dizziness or lightheadedness, primarily subjects who had received a prior PI-based regimen; this increase was not seen at timepoints other than Week 4.

## CONCLUSIONS:

- Atripla is as effective as other HAART regimens, as indicated by maintenance of high rates of virologic suppression over 48 weeks in subjects who switched therapy to Atripla or stayed on their baseline regimen. For the primary endpoint in this study, (HIV-1 RNA < 200 copies/mL at Week 48, ITT analysis set, noncompleters = failure), the proportion of responders, as defined by the TLOVR algorithm, was similar in the two treatment groups (89% responders for Atripla, 88% for SBR: difference between groups 1.1%, 95% CI -6.7% to 8.8%,  $p = 0.82$ ). Since the lower confidence boundary for the responder difference (Atripla minus SBR) was greater than -15%, the Atripla group is declared noninferior to the SBR group.
- Results for secondary virological endpoints, including PVR and rates of viral rebound, support the primary analysis and provide further evidence for the noninferiority of Atripla versus other HAART regimens.
- Baseline CD4 cell counts were high and there were no clinically relevant changes in CD4 cell counts in either treatment group.
- Atripla and other HAART regimens were generally well tolerated during this study. The majority of TEAEs were Grade 1 or 2, but Grade 3 or 4 TEAEs and NSS and rash AEs were more frequent in subjects who switched to Atripla from a PI-based regimen than from an NNRTI-based regimen.
- Baseline scores for quality of life (assessed using the SF-36v2) were similar to those for the general population, and there were no marked changes in quality of life (assessed using the SF-36v2) or treatment adherence (assessed using a VAS) for either treatment group during the study. However, differences between groups showed Atripla was an easier regimen to follow than previous regimens (assessed using PERC survey), and subjects who received Atripla preferred the medication to their previous HAART (assessed using POM survey).
- Subjects receiving Atripla had improvements in self-reported HIV symptoms in this study (sustained reductions in the proportions of subjects with diarrhea or loose bowel movements; bloating, pain, or gas in the stomach; changes in the way their body looked; and problems having sex); no changes in HIV symptoms were seen in subjects who stayed on their baseline regimen.