FINAL CLINICAL STUDY REPORT

Study Title:	**ONCE** - **O**nly **N**octurnal **C**ombination **E**valuation A Phase IV, Open-label, Prospective Observational Study to Evaluate Virological Response in Antiretroviral-Experienced HIV-1 Infected Subjects Switching to Atripla (Efavirenz/Emtricitabine/Tenofovir DF) on an Empty Stomach
Name of Test Drug:	Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (Atripla®)
Dose and Formulation:	Tablet containing 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate
Indication:	Human immunodeficiency virus type 1 infection
Sponsor:	Gilead Sciences Limited Granta Park, Abington, Cambridge, CB21 6GT United Kingdom
Study No.:	GS-EU-177-0111
Phase of Development:	Phase 4
IND No.: **EudraCT No.:**	Not applicable 2007-005769-36
Study Start Date: **Study End Date**	01 May 2008 (First Subject Screened) 20 December 2010 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Graeme Moyle, MB BS, Dip GUM Affiliation: [redacted] PPD
Gilead Responsible Medical Monitor:	Name: Dr Cham Herath Telephone: [redacted] PPD Fax: [redacted] PPD
Report Date:	25 May 2011
Previous Report Date:	22 September 2010 (Week 24 efficacy and safety summary)

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

STUDY SYNOPSIS

Study GS-EU-177-0111:
Gilead Sciences Limited
Granta Park, Abington,
Cambridge, CB21 6GT
United Kingdom

Title of Study: Study GS-EU-177-0111: **ONCE** - **O**nly **N**octurnal **C**ombination **E**valuation A Phase IV, Open-label, Prospective Observational Study to Evaluate Virological Response in Antiretroviral-Experienced HIV-1 Infected Subjects Switching to Atripla (Efavirenz/Emtricitabine/Tenofovir DF) on an Empty Stomach
Investigators: Multicenter
Study Centers: Subjects were enrolled at 5 sites in the United Kingdom (UK)
Publications: Moyle G, Orkin C, Fisher M, Taylor S, Ross J, Wang H, et al. Switching to a simplified single-tablet regimen (STR) of Atripla (ATR) from a two- or three-pill combination of the individual components (efavirenz[EFV], emtricitabine [FTC] and tenofovir DF [TDF]) maintains virological suppression: primary end point results of a 48-week, open-label study [Poster Abstract P191]. HIV Med 2010;12 (Suppl. 1):79. Moyle G, Orkin C, Fisher M, Taylor S, Ross J, Wang H, et al. Switching to a single-tablet regiment (STR) of Atripla (ATR) from a 2 or 3-pill combination of the individual components (efavirenz [EFV], emtricitabine [FTC], and tenofovir DF [TDF]) maintains virological suppression: primary endpoint results of a 48-week, open-label study [Poster P191]. 17th Annual Conference of the British HIV Association; 2011 April 6 - 8; Bournemouth, UK.
Study Period: 01 May 2008 (First subject screened) 20 December 2010 (Last subject observation)
Phase of Development: Phase 4

Objectives:

This study was conducted to assess whether there was an impact on efficacy of switching from the components of Atripla (ATR; tenofovir disoproxil fumarate [TDF] administered with food) to ATR administered on an empty stomach.

The primary objective of this study was as follows:

- To evaluate pure virologic response (PVR) rates (defined as subjects who do not have pure virologic failure [PVF] at a human immunodeficiency virus type 1 [HIV-1] ribonucleic acid [RNA] threshold of 50 copies/mL) in antiretroviral-experienced subjects receiving ATR for 48 weeks on an empty stomach

The secondary objectives of this study were as follows:

- To assess change in absolute cluster determinant 4 (CD4) cell count
- To describe safety and tolerability through the reporting of adverse events (AEs) and laboratory abnormalities
- To assess how closely dosing recommendations are adhered to through the use of a subject-reported questionnaire
- To evaluate acceptability by using 3 subject-reported questionnaires through 48 weeks: highly active antiretroviral therapy (HAART) Intrusiveness Scale (m-HIS), Perceived Ease of Regimen for Condition (PERC), and Preference of Medicine (POM)

Methodology: This was a prospective, Phase 4, open-label, UK multicenter study in virologically suppressed, HIV-1 infected subjects receiving a stable HAART regimen of efavirenz (EFV) + emtricitabine (FTC) + TDF. Eligible subjects switched treatment to ATR within 24 hours after the baseline visit, and received ATR for 48 weeks.

Postbaseline assessments were completed at Weeks 4, 12, 24, 36, and 48, and at a follow-up visit.

Number of Subjects (Planned and Analyzed):
Planned: 150
Analyzed: 115 (efficacy, safety, and outcome measures).

Inclusion criteria were expanded (protocol amendment 2), dosing restrictions regarding food were relaxed (protocol amendment 3), the recruitment period was extended, and 3 additional centers were initiated. Despite these measures, the study failed to recruit fully.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were receiving a stable HAART regimen of EFV, FTC and TDF, or Truvada and EFV for ≥ 24 weeks prior to screening. (Subjects could have been previously treated with TDF, lamivudine [3TC], and EFV or TDF, FTC, and EFV prior to switching to Truvada and EFV. They must have switched in order to simplify their HAART regimen and must not have had a treatment interruption prior to the switch). Subjects were required to have undetectable plasma HIV-1 RNA (< 50 copies/mL) at screening and ≥ 12 weeks prior to screening.

Duration of Treatment: 48 weeks
Test Product, Dose, Mode of Administration, and Batch No.: Subjects were instructed to take 1 ATR tablet, once daily on an empty stomach, at least 2 hours before or after food. Bedtime dosing was also recommended. Lot numbers: AA510B2, AA0601B3, AA0602B1, AA0602B1-A, AA0603B1
Reference Therapy, Dose, Mode of Administration, and Batch No.: Not applicable
Criteria for Evaluation: **Efficacy:** Efficacy was assessed based on HIV-1 RNA levels and CD4 and CD8 cell counts and percentages. Resistance profiles (genotyping) were to be assessed for subjects with virologic failure. **Pharmacokinetics:** No pharmacokinetic analysis was performed. **Safety:** Safety was assessed using AE documentation, laboratory analyses (hematology, chemistry [including fasting lipid profiles and fasting glucose], and urinalysis), and physical examinations. **Other:** Outcomes measures were assessed using an adherence questionnaire, the PERC questionnaire, the m-HIS, and the POM survey.

Statistical Methods: The treated analysis set was the primary analysis set for safety, efficacy, and outcomes analyses. It included subjects who were enrolled into the study and received at least 1 dose of study medication.

Efficacy: The primary efficacy endpoint was the proportion of subjects who maintained PVR at the HIV-1 RNA threshold of 50 copies/mL (Roche Amplicor Ultrasensitive Version 1.5) (PVR_{50}, lack of confirmed rebound of HIV-1 RNA level ≥ 50 copies/mL) through the Week 48 visit window. The primary endpoint, PVR_{50}, was estimated based on the Kaplan-Meier (KM) product limit method. The 95% confidence interval (CI) of PVR_{50} was calculated for the KM point estimate at Week 48. Secondary PVR endpoints were analyzed in a similar manner to the primary endpoint.

Atripla (empty stomach) was noninferior to EFV+FTC+TDF (without regards to meals) if the lower bound of a 2-sided 95% CI for PVR_{50} was at least 82.5%. The historic rate was based on subjects taking individual components of EFV+FTC+TDF without regards to meals in Study GS-01-934 after achieving PVR_{50}. It was assumed the response rate observed for subjects receiving ATR on an empty stomach is identical to subjects receiving EFV+FTC+TDF without regards to meals.

Percentages of subjects with plasma HIV-1 RNA < 50 and < 400 copies/mL were summarized using missing = failure (M=F; by visit), missing = excluded (M=E; by visit), and last nonmissing postbaseline observation carried forward (LOCF; Weeks 24 and 48) methods.

Absolute values for CD4 cell count, CD4%, CD8 cell count, and CD8%, and changes from baseline were summarized by visit. Statistical significance of the change from baseline was assessed using the Wilcoxon signed rank test at Week 48.

HIV-1 genotyping (resistance testing) was to be done at the conclusion of the study for subjects determined to be virologic failures and with HIV-1 RNA ≥ 400 copies/mL.

Pharmacokinetics: No pharmacokinetic analysis was performed.

Safety: All safety endpoints summarized using descriptive statistics. Data collected up to the date of last dose of study drug plus 30 days were included. Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 13.1.

Other: Subject-reported adherence was summarized categorically by visit using the numbers of days with missed doses in the past 30 days and past 7 days. Other outcomes research endpoints were summarized; changes from baseline were summarized when relevant using appropriate statistical tests.

SUMMARY – RESULTS:

Subject Disposition and Demographics: A total of 115 subjects were enrolled and received ATR in this study. Ninety-seven subjects completed 48 weeks of study treatment and 18 subjects prematurely discontinued. The most common reason for study discontinuation was protocol violation (9 subjects). No subjects discontinued study drug due to lack of efficacy.

Subjects in this study were predominantly male (83.5%) and had a mean age of 41 years (minimum 19 years, maximum 61 years). Overall, 75.7% were white and 20.0% were black or of African heritage.

Efficacy Results: The PVR_{50} through Week 48 was 99.0% (95% CI: 97.1%, 100.0%). Since the lower bound of the 95% CI was higher than 82.5%, ATR dosed on an empty stomach is noninferior to a regimen of EFV+FTC+TDF dosed without regards to meals. Identical results for PVR_{50} were seen in the sensitivity analysis to assess the effect of censoring on the estimate of the standard error of PVR at Week 48.

The PVR_{50} through Week 24 and the PVR_{400} through Weeks 24 and 48 were each 100% (the asymptotic 95% CIs were not estimable).

The percentages of subjects with HIV-1 RNA < 50 and < 400 copies/mL were high throughout the study. The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were 82.6%, 99.1%, and 99.0% when assessed using M=F, LOCF, and M=E methods, respectively. No HIV-1 RNA values ≥ 400 copies/mL were reported during the study.

There were increases in CD4 cell count and CD4% during the study. The median CD4 cell count at baseline was 415 cells/μL and the median change from baseline at Week 48 was 60 cells/μL (n = 95, p < 0.001). The median CD4% at baseline was 26.7% and the median change from baseline at Week 48 was 2.5% (n = 95, p < 0.001, Wilcoxon signed rank test).

There were small and inconsistent changes in CD8 cell count during the study (the median change from baseline at Week 48 was 0 cells/μL, n = 95, p = 0.98). There were small decreases in CD8% during the study. The median CD8% at baseline was 46.8% and the median change from baseline at Week 48 was –2.4% (n = 95, p < 0.001).

No subjects met criteria for genotyping to be performed.

Pharmacokinetic Results: No pharmacokinetic analysis was performed.

Safety Results: Atripla was generally well tolerated during this study. No subjects died. Serious adverse events (SAEs) were reported for 4 subjects (3.5%); no SAEs were considered related to study drug by the investigator. Adverse events that resulted in study drug discontinuation were reported for 2 subjects (1.7%). At least 1 AE was reported for 97 subjects (84.3%). Adverse events considered related to study drug by the investigator were reported for 19 subjects (16.5%). Grade 2, 3, or 4 AEs were reported for 60 subjects (52.2%); Grade 2, 3, or 4 AEs were considered related to study drug for 6 subjects (5.2%). Grade 3 or 4 AEs were reported for 7 subjects (6.1%); Grade 3 or 4 AEs were considered related to study drug by the investigator for 1 subject (0.9%). No pregnancies were reported.

Adverse events were most frequently reported in the following system organ classes (SOCs): infections and infestations (61 subjects, 53.0%); gastrointestinal disorders (36 subjects, 31.3%); and psychiatric disorders (25 subjects, 21.7%). The most frequently reported AEs were upper respiratory tract infection (16 subjects, 13.9%), diarrhea (15 subjects, 13.0%), nasopharyngitis (14 subjects, 12.2%), and headache (14 subjects, 12.2%). The majority of the AEs reported in the study were mild (Grade 1) or moderate (Grade 2) in severity. No Grade 3 or 4 AE was reported for more than 1 subject.

Adverse events considered related to study drug by the investigator and reported for more than 1 subject were abnormal dreams (reported for 6 subjects); diarrhea (reported for 5 subjects); and nausea, dizziness and nightmare (each reported for 2 subjects). Depression ([redacted]) was the only Grade 3 or 4 AE considered related to study drug by the investigator.

No bone fractures were reported. No renal AEs were reported that were considered related to study drug by the investigator.

No AEs considered related to mitochondrial toxicity were reported.

One AE (cholecystitis) was reported in the hepatobiliary disorders SOC, and hepatitis C was reported as an AE for 1 subject. The AEs were Grade 2 in severity and were not considered related to study drug by the investigator. No high-grade (Grade 3 or 4) hepatic enzyme elevations were reported.

Adverse events in the nervous system disorders SOC were reported for 20 subjects (17.4%). The most frequently reported nervous system AEs were headache (14 subjects) and dizziness (4 subjects). Nervous system AEs considered related to study drug were reported for 4 subjects (3.5%); the AEs were dizziness (2 subjects), lethargy (1 subject), and dysgeusia (1 subject). Headache (1 subject) and neuralgia (1 subject) were reported with Grade 3 severity.

Adverse events in the psychiatric disorders SOC were reported for 25 subjects (21.7%). The most frequently reported psychiatric AEs were depression, insomnia, and abnormal dreams (each reported for 6 subjects). Psychiatric AEs considered related to study drug were reported for 11 subjects (9.6%); the AEs were abnormal dreams (6 subjects); nightmare (2 subjects); and anxiety, depression, mood swings, and depressed mood (each reported for 1 subject). Depression was reported with Grade 3 severity for [redacted PPD]; the AE resulted in study drug discontinuation.

No Grade 3 or 4 AEs were reported in the skin and subcutaneous tissue disorders SOC.

The SAEs reported were abdominal pain, cellulitis, diffuse large B-cell lymphoma Stage II, and asthma; each SAE was reported for 1 subject.

The AEs that resulted in study drug discontinuation were fatigue and depression, each reported for 1 subject. The AE of depression (Grade 3; ongoing; [redacted PPD]) was considered related to study drug by the investigator.

There were no clinically relevant changes from baseline in median values for hematology or clinical chemistry parameters, including no clinically relevant changes in serum creatinine, serum phosphorus, creatinine clearance (Cockcroft-Gault formula), glomerular filtration rate (Modification of Diet in Renal Disease method), or fasting lipid parameters. Treatment-emergent Grade 3 or 4 abnormalities were reported for 9 subjects (maximum Grade 3 for 6 subjects and maximum Grade 4 for 3 subjects), most frequently for creatine kinase (3 subjects) and gamma glutamyltransferase (3 subjects).

There were no clinically relevant changes in body weight, body mass index, or vital signs (heart rate, blood pressure, respiration, and temperature) during the study.

Other: Self-reported adherence was high. The percentages of subjects who reported having missed medication on < 2 days in the last 30 days was 96.5% at baseline and 90.8% at Week 48. The percentages of subjects who reported having missed no medication in the last 7 days was 96.5% at baseline and 95.9% at Week 48. Study drug adherence was high when assessed using pill counts (median 100%). A total of 108 subjects (93.9%) had adherence rates ≥ 95% during the study.

Subjects in this study considered ATR an easier regimen to follow than their previous HIV regimen (assessed using the PERC survey). The percentage of subjects who considered their regimen very easy to take increased from 70.2% at baseline to 91.8% at Week 48 ($p < 0.0001$).

Study medication acceptability was good at baseline (assessed using the m-HIS index score) and improved during the study for subjects who received ATR. There was a statistically significant reduction (improvement) in overall m-HIS index score from baseline to Week 48 (median [first and third interquartiles, Q1, Q3] change 0.0 [−0.3, 0.1]; mean [SD] change −0.1 [0.59], $p = 0.006$).

The majority of subjects who received ATR preferred it to their previous medication (assessed using the POM questionnaire). At Week 48, 68.4% of subjects considered ATR to be much better than their previous regimen, and 8.2% of subjects considered ATR to be slightly better than their previous regimen ($p < 0.001$).

CONCLUSIONS:

- The PVR rate was high in antiretroviral-experienced subjects receiving ATR for 48 weeks dosed once daily on an empty stomach. The PVR_{50} through Week 48 was 99.0% (95% CI: 97.1%, 100.0%). Since the lower bound of the 95% CI was higher than 82.5%, ATR dosed on an empty stomach is noninferior to a regimen of EFV+FTC+TDF dosed once daily without regards to meals.
- Immunologic benefits of ATR dosed on an empty stomach were demonstrated in the increases in CD4 cell count during the study (baseline median 415 cells/μL; median change from baseline at Week 48 of 60 cells/μL, $p < 0.001$).
- Atripla was generally well tolerated in this study. No treatment-emergent SAEs considered related to ATR were reported. Two subjects experienced AEs that resulted in discontinuation of ATR (1 event, depression, was considered related to study drug by the investigator). The most frequently reported AEs were upper respiratory tract infection, diarrhea, nasopharyngitis, and headache.
- Self-reported adherence was high. Similar percentages of subjects reported missing medication in the last 7 days when assessed at baseline and at Week 48. There was a small reduction in the percentages of subjects who reported missing medication in the last 30 days when assessed at Week 48 compared to baseline (90.8% at Week 48 compared to 96.5% at baseline). No additional data were collected in relation to protocol-defined dosing recommendations.
- Subjects preferred ATR to their previous regimen, and found ATR easier to take and less intrusive on their life than their previous regimen, as assessed using subject-reported questionnaires.