



## FINAL CLINICAL STUDY REPORT

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**Study Title:** Switch to a completely ONce daily Regimen containing Emtricitabine/Tenofovir – Fixed Dose Combination plus Third QD partner: “SONETT”

**Name of Test Drug:** Emtricitabine/tenofovir disoproxil fumarate

**Dose and Formulation:** 200 mg/300 mg tablet

**Indication:** Human immunodeficiency virus Type 1

**Sponsor:** Gilead Sciences GmbH  
Fraunhoferstr. 17  
82152 Martinsried  
Germany

**Study No.:** GS-DE-164-0106

**Phase of Development:** Phase 3

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

**Study Start Date:** 17 January 2005 (First Subject Screened)  
**Study End Date:** 22 January 2007 (Last Subject Observation)

**Principal or Coordinating Investigator:** Name: PD Dr Keikawus Arastéh  
Affiliation: EPIMED GmbH

**Gilead Responsible Medical Monitor:** Name: Dr med Thomas Mertenskoetter

**Report Date:** 01 June 2007

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### 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 GmbH**  
**Fraunhoferstr. 17**  
**82152 Martinsried**  
**Germany**

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**Title of Study:** Switch to a completely Once daily Regimen containing Emtricitabine/Tenofovir – Fixed Dose Combination plus Third QD partner: “SONETT”

**Investigators:** K Arastéh, B Kuhlmann, L Weitner

**Study Centers:** Three centers in Germany

**Publications:**

Weitner L, Fenske S, Kuhlmann B, Freiwald M, Ebrahimi R, Gallo L, et al. Switch to a completely once daily regimen containing Emtricitabine/Tenofovir-fixed dose combination plus Third QD partner: 24 weeks interim analysis of the SONETT trial [abstract-no. 950145-64]. Eighth International Congress on Drug Therapy in HIV Infection; 2006 November 12–16; Glasgow, UK.

**Study Period:**

17 January 2005 (First subject screened)  
22 January 2007 (Last subject observation)

**Phase of Development:** Phase 3

**Objectives:**

The primary objective of this study was as follows:

- To assess efficacy of a treatment switch from a regimen with zidovudine and lamivudine plus a third partner to a once-daily regimen containing the fixed-dose combination of tenofovir DF and emtricitabine in combination with a third once-daily partner in HIV infected subjects

The secondary objectives of this study were as follows:

- To assess the safety of a treatment switch from a regimen with zidovudine and lamivudine plus a third partner to a once-daily regimen containing the fixed-dose combination of tenofovir DF and emtricitabine in combination with a third once-daily partner in HIV infected subjects
- To define the resistance profile at failure
- Assessment of quality of life

**STUDY SYNOPSIS (CONTINUED)**

**Methodology:** A Phase 3, prospective, nonrandomized, single-group, open-label, 48-week, pilot study. At baseline, subjects were switched from their existing HAART regimen to a once-daily regimen containing the emtricitabine/tenofovir DF (200 mg/300 mg) fixed-dose combination tablet (Truvada), and a third once-daily partner. Subjects received study drug for 48 weeks and were assessed for efficacy and safety at Weeks 4, 12, 24, 36, and 48.

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

Planned: 50

Analyzed: Efficacy 51

Safety 52

**Diagnosis and Main Criteria for Inclusion:** Virologically-suppressed (HIV-1 RNA concentration < 50 copies/mL), HIV infected adults receiving zidovudine- and lamivudine-containing HAART (for > 3 months), who were experiencing side effects, adherence problems, or who had a need for a once-daily regimen

**Duration of Treatment:** 48 weeks

**Test Product, Dose, Mode of Administration, and Batch No.:** Emtricitabine/tenofovir DF tablets (200 mg/300 mg) orally, once daily, with or without food. Lot numbers V301B2, V402B1, and V406B1.

**Reference Therapy, Dose, Mode of Administration, and Batch No.:** Not applicable

**Criteria for Evaluation:**

**Efficacy:** HIV ribonucleic acid (RNA) concentration; CD4 and CD8 cell counts; quality of life (SF-12<sup>®</sup> Health Survey); HIV genotyping for subjects who were considered virologic failures.

**Safety:** Adverse events (AEs) and serial laboratory tests

## STUDY SYNOPSIS (CONTINUED)

### Statistical Methods:

**Efficacy:** The proportions of subjects included in ITT analysis set with viral load < 50 copies/mL were calculated by study visit. The primary analysis of the primary efficacy endpoint (Week 48) was performed using a missing = failure approach. Secondary analyses were performed with missing data excluded, and with early discontinuations treated as failure and other missing data excluded. HIV-1 RNA concentrations were summarized by categories and by visit. CD4 and CD8 cell counts and changes from baseline in CD4 and CD8 cell counts were calculated and summarized.

For quality of life (SF-12, Version 1), the mental composite score, and physical composite score were summarized for each of the three subgroups (switched for relief of symptoms, switched to utilize a simpler regimen, or both), as well as for entire ITT analysis set

**Safety:** Safety characteristics were summarized using descriptive statistics, with changes from baseline for clinical laboratory parameters. Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 9.1. All safety data were listed.

### SUMMARY – RESULTS:

**Efficacy Results:** Subjects switched from a HAART regimen containing twice daily zidovudine/lamivudine to a once-daily regimen of emtricitabine/tenofovir DF + third partner maintained virologic suppression during 48 weeks of treatment in this study. Seventy-eight percent of subjects (40/51 subjects) had plasma HIV-1 RNA concentrations < 50 copies/mL at Week 48 using the missing = failure approach. For the missing = excluded, and early discontinuation = failure plus missing = excluded approaches, 98% (40/41 subjects) and 80% (40/50 subjects) of subjects had plasma HIV-1 RNA concentrations < 50 copies/mL at Week 48. No subjects had HIV-1 RNA concentrations reported at study visits that were  $\geq$  400 copies/mL, and no subjects met the criterion for loss of virologic response during the study. No statistically significant changes from baseline in CD4 and CD8 cell counts were reported.

No statistically significant changes from baseline in SF-12 physical or mental composite scores were reported during the study.

## STUDY SYNOPSIS (CONTINUED)

**Safety Results:** The regimen of emtricitabine/tenofovir DF + third partner was well tolerated in this study population of HIV-1 infected subjects. There were no deaths during the study. Three subjects reported SAEs during the study; none of the events was considered related to study drug. Three subjects experienced AEs that resulted in permanent discontinuation of study drug; two events that resulted in permanent discontinuation were considered related to study drug (renal pain and drug hypersensitivity).

Treatment-emergent AEs were reported for 45 of 52 subjects (87%); the most frequently reported events were nasopharyngitis (11 subjects), diarrhoea (seven subjects), and gastroenteritis (five subjects). No Grade 4 treatment-emergent AEs were reported during the study. Five subjects had six Grade 3 AEs reported (inguinal hernia, hepatic failure, giardiasis, contusion, whiplash injury, and depression); none of these AEs was considered related to study drug. Seven subjects had 13 AEs reported that were considered related to study drug by the investigator. No individual event was reported for more than one subject.

Renal and urinary disorders were reported in four subjects (urethral pain in two subjects, and dysuria and renal pain each in one subject); renal pain in one subject was considered related to study drug by the investigator.

One subject had a bone fracture reported during the study; the fracture was considered not related to study drug by the investigator.

Six subjects had skin and subcutaneous tissue disorders reported during the study (dermatitis allergic, pruritus, and rash each in two subjects; acne, hyperhidrosis, and rosacea each in one subject); one AE of rash was considered related to study drug by the investigator.

Grade 3 or 4 elevations were reported for the following analytes: total bilirubin, ALT, and lipase, each in two subjects; AST in one subject. Grade 3 or 4 decreases were reported for the following analytes: blood glucose in two subjects; hemoglobin and white blood cell count each in one subject.

There were no clinically relevant changes in serum creatinine or serum phosphorus during the study. No Grade 2, 3, or 4 serum creatinine abnormalities were reported. No Grade 3 or 4 serum phosphorus abnormalities were reported; Grade 2 hypophosphatemia was reported for four subjects. There were small, statistically significant decreases from baseline in creatinine clearance (Cockcroft Gault method, at Weeks 4, 12, 24, and 36) and eGFR (by MDRD formula, at Weeks 4, 12, and 24). These changes were not considered clinically relevant, and changes from baseline to Week 48 in creatinine clearance and eGFR were not statistically significant.

One subject was classed as having moderate renal disease (MDRD Stage 3) during the study: Subject 1018-2013 had an eGFR of 55.9 mL/min/1.73 m<sup>2</sup> at Week 24. The subject had mild (MDRD Stage 2) renal impairment at baseline and at Weeks 4, 12, 36, and 48. This subject's serum creatinine was in the normal range at baseline (1.2 mg/dL, normal range 0.5-1.2 mg/dL) but was elevated at all subsequent visits (1.3–1.5 mg/dL, Grade 1).

**STUDY SYNOPSIS (CONTINUED)**

**Safety Results (continued):** There were statistically significant increases in hemoglobin concentration and red blood cell count from baseline at all postbaseline time points. At Week 48, the median change from baseline in hemoglobin concentration was 0.8 g/dL (interquartile range 0.3–1.3 g/dL,  $p < 0.0001$ ). Median values for red blood cell count at baseline (3.9 cells/pL) were lower than reference ranges. The increases from baseline most likely represent an improvement with the switch away from zidovudine-containing therapy.

**CONCLUSIONS:**

- Subjects switched from a HAART regimen containing twice daily zidovudine/lamivudine to a once-daily regimen of emtricitabine/tenofovir DF + third partner maintained virologic suppression during 48 weeks of treatment in this study. No subjects had HIV-1 RNA concentrations reported at study visits that were  $\geq 400$  copies/mL, and no subjects met the criterion for loss of virologic response during the study. No statistically significant changes from baseline in CD4 and CD8 cell counts were reported.
- The regimen of emtricitabine/tenofovir DF + third partner was well tolerated in this study population of HIV-1 infected subjects. There were no deaths during the study. Three subjects reported SAEs during the study; none of the events was considered related to study drug. Three subjects experienced AEs that resulted in permanent discontinuation of study drug; two events that resulted in permanent discontinuation were considered related to study drug (renal pain and drug hypersensitivity).
- No statistically significant changes were seen in quality of life as measured using the SF-12 (Version 1) health survey.