



ABBREVIATED CLINICAL STUDY REPORT

Study Title: A Phase 4, Single-Arm Study To Evaluate the Safety, Antiretroviral Activity and Pharmacokinetics of Tenofovir Disoproxil Fumarate in Combination with Emtricitabine in HIV-1 Infected Patients Experiencing Various Degrees of Renal Impairment

Name of Test Drugs, Dose and Formulation: Emtricitabine (200 mg capsules), tenofovir disoproxil fumarate (300 mg tablets), and emtricitabine/tenofovir disoproxil fumarate (200 mg/300 mg combination tablet); dose according to degree of renal impairment

Indication: Human immunodeficiency virus Type 1

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive, Foster City, CA 94404
USA

Study No.: GS-104-0235

Phase of Development: Phase 4

IND No.: 52,849
EudraCT No.: 2004-000309-23

Study Start Date: 25 October 2004 (First Subject Screened)
Study End Date: 13 March 2006 (Last Subject Observation)

Principal or Coordinating Investigator: Name: Gerald Pierone, MD
Affiliation: Treasure Coast Infectious Disease Consultants

Gilead Responsible Medical Monitor (Poststudy Conduct): Name: Elsa Mondou, MD

Report Date: 10 August 2007
Synopsis Date: 17 March 2008

CONFIDENTIAL AND PROPRIETARY INFORMATION

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

STUDY SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 4, Single-Arm Study To Evaluate the Safety, Antiretroviral Activity and Pharmacokinetics of Tenofovir Disoproxil Fumarate in Combination with Emtricitabine in HIV-1 Infected Patients Experiencing Various Degrees of Renal Impairment
Investigators: Multicenter
Study Centers: Four centers enrolled subjects, three in the United States, and one in France
Publications: None
Study Period: 25 October 2004 (First subject screened) 13 March 2006 (Last subject observation)
Phase of Development: Phase 4
Objectives: The primary objective of this study was as follows: <ul style="list-style-type: none">• To evaluate the safety and tolerability of tenofovir following administration of tenofovir disoproxil fumarate (TDF, tenofovir DF) 300 mg for 48 weeks in human immunodeficiency virus (HIV) infected subjects experiencing various degrees of renal impairment The secondary objectives of this study were as follows: <ul style="list-style-type: none">• To evaluate the safety and tolerability of emtricitabine following administration of emtricitabine 200 mg for 48 weeks in HIV infected subjects experiencing various degrees of renal impairment• To evaluate the efficacy of tenofovir DF in combination with emtricitabine in renally-impaired HIV infected subjects• To evaluate the pharmacokinetics of tenofovir and emtricitabine in renally-impaired HIV infected subjects

STUDY SYNOPSIS (CONTINUED)

Methodology: This was an open-label, single-group study in treatment-naive or treatment-experienced HIV Type 1 (HIV-1) infected subjects with stable renal disease. Treatment-naive subjects received a fixed regimen of emtricitabine, tenofovir DF, and efavirenz for 48 weeks. Treatment-experienced subjects were switched from their existing stable regimen (defined as stable on their existing regimen for at least 3 months and a screening plasma HIV-1 ribonucleic acid [RNA] concentration of ≤ 50 copies/mL) to emtricitabine, tenofovir DF, and either to remain on their current non-nucleoside reverse transcriptase inhibitor or to remain on their current protease inhibitor for 48 weeks. Subjects with mild through severe renal impairment received emtricitabine 200 mg and tenofovir DF 300 mg in a fixed-dose combination tablet. The frequency of dosing differed for each renal impairment group, as summarized below.

	Renal Impairment Group			
	Mild	Moderate	Severe	ESRD ^a
Calculated Creatinine Clearance (mL/min) ^b	≥ 50 and < 80	≥ 30 and < 50	≥ 15 and < 30	Requiring hemodialysis
Study Drugs				
Tenofovir DF 300 mg Tablet	Not applicable	Not applicable	Not applicable	Every 7 days ^c
Emtricitabine 200 mg Capsule	Not applicable	Not applicable	Not applicable	Every 96 hours ^d
Emtricitabine 200 mg and tenofovir DF 300 mg Combined Tablet	Every 24 hours	Every 48 hours	Every 72 hours	Not applicable
Efavirenz 600 mg Tablet ^e	Every 24 hours	Every 24 hours	Every 24 hours	Every 24 hours

a End stage renal disease

b Calculated creatinine clearance using the Cockcroft Gault equation and ideal body weight [IBW], unless total body weight [TBW] was less than IBW in which case TBW was used

c Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration each. Tenofovir DF was administered following completion of dialysis.

d If dosing on day of dialysis, emtricitabine was administered after dialysis.

e Dosing regimen for efavirenz. Subjects remaining on a protease inhibitor or non nucleoside reverse transcriptase inhibitor received them in accordance with dosing instructions in the package insert.

Number of Subjects (Planned and Analyzed):

Planned: 32 to 40 evaluable HIV infected subjects with varying degrees of renal impairment, plus 12 subjects (HIV-1 infected not receiving tenofovir DF, preferred, or non-HIV-1 infected) with severe renal impairment or undergoing hemodialysis, matched for sex and age, as a control for bone density assessments

Enrolled: 8 HIV infected subjects, zero control subjects

Evaluable: Efficacy, 8 HIV infected subjects
 Pharmacokinetics, 8 HIV infected subjects
 Safety, 8 HIV infected subjects

STUDY SYNOPSIS (CONTINUED)

Diagnosis and Main Criteria for Inclusion: Male and nonpregnant female HIV-1 infected subjects, aged 18 to 80, with stable renal impairment. Subjects were either: antiretroviral therapy-naive, requiring antiretroviral treatment, with HIV-1 RNA concentration > 400 copies/mL; or antiretroviral therapy-experienced, on a stable antiretroviral regimen for at least 3 months, with HIV-1 RNA concentration \leq 50 copies/mL at screening.

Duration of Treatment: 48 weeks

Test Product, Dose, Mode of Administration, and Batch No.:

Tenofovir DF 300 mg tablet administered orally: Lots J208D1 and J408B1.

Emtricitabine 200 mg capsule administered orally: Lots W304A1 and W306A1.

Emtricitabine 200 mg and tenofovir DF 300 mg combined tablet: Lots V301B2, V402B1, and V402B1-1.

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

Criteria for Evaluation:

Efficacy: Plasma HIV-1 RNA concentrations, CD4 cell counts, and HIV-1 genotyping.

Pharmacokinetics: The following pharmacokinetic parameters were determined for emtricitabine and tenofovir in plasma: C_{max} , C_{min} , T_{max} , AUC_{tau} , Avg Daily AUC, $T_{1/2}$, λ_z , and CL/F.

Safety: Adverse events (AEs), clinical laboratory tests (including renal function assessments), vital signs, physical examinations, and bone density assessments.

Statistical Methods:

Statistical analyses in this study were based on available data rather than the protocol-specified analyses, since only eight HIV infected subjects were enrolled.

Efficacy: Efficacy analyses were conducted on all subjects in the intent-to-treat (ITT) analysis set. The proportion of subjects with HIV RNA concentrations < 50 copies/mL was summarized by renal impairment group and overall. Changes from baseline in CD4 cell count and percentage were summarized using descriptive statistics by renal impairment group and overall.

STUDY SYNOPSIS (CONTINUED)

Statistical Methods (continued):

Pharmacokinetics: Steady-state pharmacokinetic parameters were computed for all subjects in the pharmacokinetic analysis set. Pharmacokinetic parameters were estimated for individual subjects using standard noncompartmental methods (WinNonlin[®], Version 5.0.1). Plasma concentrations and pharmacokinetic parameters of tenofovir and emtricitabine were presented for each subject and descriptive statistics (sample size, arithmetic mean, standard deviation, coefficient of variation [% CV], median, minimum, maximum, geometric mean and 95% confidence intervals, mean and standard deviation of log) were calculated and tabulated per sampling time by dosage regimen. Additional summary statistics were calculated excluding data when the dosage regimen administered was not appropriate for the subject's renal function (i.e., calculated creatinine clearance) on the day of pharmacokinetic evaluation. Mean and median concentration-time profiles of tenofovir and emtricitabine were plotted by dosage regimen.

Safety: Safety characteristics were summarized using descriptive statistics, with changes from baseline for 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: Plasma HIV-1 RNA concentrations remained < 50 copies/mL after switching NRTIs to emtricitabine and tenofovir DF in all treatment-experienced subjects, except for one subject who had a plasma HIV-1 RNA concentration of 252 copies/mL at Week 48. Plasma HIV-1 RNA concentrations declined from 32,200 copies/mL at baseline to < 50 copies/mL at Week 4 and at every subsequent study visit in the only antiretroviral-naive subject enrolled.

STUDY SYNOPSIS (CONTINUED)

Pharmacokinetic Results: For four subjects with mild renal impairment on the day of pharmacokinetic evaluation, median tenofovir C_{max} , C_{min} , and AUC_{tau} were in good agreement with predicted values based on the single-dose data used to develop the current dosage adjustment regimens for renal impairment. The highest C_{max} , C_{min} , and AUC_{tau} observed were approximately 2-fold higher than the maximum predicted values; this was not unexpected given that the subject for whom these values were reported had a CL_{cr} of 51 mL/min, just above the upper cutoff for the moderate renal impairment group. For two subjects with moderate renal impairment on the day of pharmacokinetic evaluation, median C_{max} , C_{min} , and AUC_{tau} were about 2-fold higher than predicted median values, and the highest C_{max} , C_{min} , and AUC_{tau} were slightly higher than the maximum predicted values. For one subject with severe renal impairment on the day of pharmacokinetic evaluation, C_{max} , C_{min} , and AUC_{tau} were within the predicted range.

Emtricitabine C_{max} , C_{min} , and AUC_{tau} in subjects with mild, moderate, or severe renal impairment on the day of pharmacokinetic evaluation were in reasonable agreement with predicted values based on the single-dose data used to develop the current dosage adjustment regimens for renal impairment.

Safety Results: Tenofovir DF and emtricitabine were generally well tolerated in this study. There were no deaths during the study. Four subjects completed 48 weeks of treatment and four discontinued; all four subjects who discontinued experienced decreased renal function (increased serum creatinine or $\geq 20\%$ decrease in calculated creatinine clearance [CL_{cr}] from baseline) of varying etiology, as follows. Two subjects discontinued study drug due to AEs; renal impairment and glomerular filtration rate decreased, both considered related to study drug by the investigator.

Treatment-emergent Grade 3 and 4 abnormalities in clinical chemistry analytes were seen only in subjects initially assigned to the moderate renal impairment group; no Grade 3 or 4 abnormalities in hematology or urinalysis analytes were seen. Treatment-emergent Grade 4 abnormalities were reported for serum bicarbonate and serum glucose (both for the same subject). Treatment-emergent Grade 3 abnormalities were reported for creatinine (two subjects), and amylase, glucose, and triglycerides (each in one subject); all Grade 3 abnormalities were classed as marked laboratory abnormalities.

There were no clinically relevant findings reported during the study for bone mineral density or hormonal profiles, or for changes in vital signs, body weight, and physical examinations.

STUDY SYNOPSIS (CONTINUED)

CONCLUSIONS: Tenofovir DF and emtricitabine were generally well tolerated during this study; safety findings were generally consistent with those anticipated in this small population of renally-impaired subjects.

For this limited dataset, median tenofovir and emtricitabine pharmacokinetics in subjects with varying degrees of renal impairment were in reasonable agreement with predicted values based on the single-dose data used to develop the current dosage adjustment regimens. While the majority of subjects fell within the range of predicted exposures, there were exposures outside predicted ranges in subjects with calculated CL_{cr} in the borderline range between impairment groups.

From the limited data available from this study, it is not possible to make conclusions regarding the planned efficacy objectives.