



SYNOPTIC CLINICAL STUDY REPORT

Study Title:	B oosted A tazanavir and T ruvada Given O nce-Daily – the B ATON Study: A Phase 4, Prospective, Open-Label, Multicenter Study of the Safety, Efficacy, and Adherence in HIV-Infected, Antiretroviral-Naive Subjects Treated with a Simple Once-Daily Regimen
Name of Test Drug:	Emtricitabine/Tenofovir disoproxil fumarate + Atazanavir/ritonavir
Dose and Formulation:	Daily oral doses: Emtricitabine 200 mg; Tenofovir DF 300 mg; Atazanavir 300 mg; Ritonavir 100 mg
Indication:	HIV
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-164-0115
Phase of Development:	Phase 4
IND No.:	N/A
EudraCT No.:	N/A
Study Start Date:	02 September 2005 (First Subject Screened)
Study End Date:	03 January 2007 (Last Subject Observation)
Principal or Coordinating Investigator:	Richard Elion, MD Clinical Alliance for Research & Education - Infectious Diseases (CARE-ID) 2311 M St. NW, Suite 401 Washington, DC 20037
Gilead Responsible Medical Monitor:	Name: John Flaherty, Pharm D Telephone: 650-522-5592 Fax: 650-522-5557
Report Date:	25 March 2008
Previous Report Date(s):	N/A

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: **B**oosted **A**tazanavir and **T**ruvada Given **O**nce-Daily – the **BATON** Study: A Phase 4, Prospective, Open-Label, Multi Center Study of the Safety, Efficacy, and Adherence in HIV-Infected, Antiretroviral-Naive Subjects Treated with a Simple Once-Daily Regimen

Investigators: Multicenter

Study Centers: 21 centers in US enrolled 102 subjects.

Publications: Elion R, Cohen C, Ward D, Ruane P, Reddy S, Ebrahimi R, et al. Evaluation of the efficacy, safety, pharmacokinetics, adherence, and treatment satisfaction with boosted atazanavir and fixed-dose Emtricitabine/Tenofovir DF (Truvada) given once-daily in HIV infected, antiretroviral naive subjects: Final results of BATON [Poster #P7.3/20]. Presented at 11th European AIDS Conference, Madrid, 2007.

Study Period:

02 September 2005 (First subject screened)
03 January 2007 (Last subject observation)

Phase of Development: Phase 4

Objectives: The primary objective of this study was as follows:

To determine the safety and efficacy (viral load suppression and CD4 changes) of a simple, once-daily (QD) antiretroviral (ARV) regimen consisting of a fixed-dose combination tablet containing emtricitabine and tenofovir disoproxil fumarate (DF) (Truvada) combined with the protease inhibitor (PI) atazanavir boosted with ritonavir (ATV/r).

The secondary objectives of this study were as follows:

- To evaluate fasting glucose, insulin, C-peptide, and lipid panel (total cholesterol, high- and low-density lipoprotein cholesterol [HDL, LDL], and serum triglycerides [TG]) in subjects receiving Truvada (emtricitabine and tenofovir) and boosted atazanavir.

To evaluate adherence to a QD ARV regimen of Truvada and boosted atazanavir.

- To evaluate steady-state plasma pharmacokinetics of Truvada and atazanavir in study subjects receiving Truvada and boosted atazanavir.

STUDY SYNOPSIS (CONTINUED)

Methodology: This was a 48-week, prospective, single-arm, open-label pilot study to assess the safety, tolerability, efficacy, pharmacokinetics, and adherence of a once-daily regimen of fixed-dose emtricitabine/tenofovir DF (FTC/TDF) 200 mg/300 mg and ATV 300 mg (given as two 150-mg capsules) boosted with 100 mg of ritonavir. Subjects were stratified according to screening HIV-1 RNA levels (two subgroups: $\geq 100,000$ copies/mL and $< 100,000$ copies/mL), where no more than 60% of the planned subjects were to be in a subgroup.

Number of Subjects (Planned and Analyzed):

Planned: 100 subjects

102 subjects were enrolled, 100 were treated and had post-baseline data.

Analyzed: 100 subjects (60 with baseline HIV-1 RNA $< 100,000$ copies/mL; 40 with baseline HIV-1 RNA $\geq 100,000$ copies/mL)

Diagnosis and Main Criteria for Inclusion: Subjects were HIV-1-infected, ARV-treatment-naive adults (≥ 18 years of age) with plasma HIV-1 RNA levels ≥ 1000 copies/mL and adequate renal function (creatinine clearance ≥ 50 mL/min, calculated using the Cockcroft-Gault [C-G] equation). There was no CD4 count restriction.

Duration of Treatment: 48 weeks

Test Product, Dose, Mode of Administration, and Batch No.: All drugs were administered orally.

Test Product	Lot Numbers
FTC 200 mg/Tenofovir DF 300 mg (Truvada [®])	V306B2 V406B1 V403B1
ATV 150 mg (Reyataz [®])	5K3104 5E3039
Ritonavir 100 mg (Norvir [®])	247022E21

Reference Therapy, Dose, Mode of Administration, and Batch No.: N/A

STUDY SYNOPSIS (CONTINUED)

Criteria for Evaluation: Within 28 days of screening, subjects were dispensed medication at their baseline visit. They returned to the clinic at Weeks 4, 12, 24, 36, and 48 (or following early study drug discontinuation) for drug dispensation and the following assessments:

Efficacy: CD4 cell counts and measurement of plasma HIV-1 RNA levels (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostics); HBV DNA and HBV serologies (if HBsAg+ at screening); stored samples for resistance analysis (viral genotyping and phenotyping).

Pharmacokinetics: Samples for 24-hour plasma trough concentrations of FTC, tenofovir, atazanavir, ritonavir (Weeks 4, 24, and 48 only).

Adherence and Subject Satisfaction: Pill counts and subject questionnaires.

Safety: AEs, hematology, serum chemistry profile, urinalysis, fasting lipid panel, glomerular filtration rate (GFR) (estimated by the C-G formula for creatinine clearance and by the abbreviated Modified Diet in Renal Disease [MDRD] equation), vital signs, physical examination, and concomitant medications.

Statistical Methods:

Efficacy: The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA levels < 50 copies/mL at 48 weeks (missing = failure). The secondary HIV-1 RNA efficacy endpoints included percentages of subjects (1) who had a confirmed response < 50 copies/mL (two consecutive values or a single value at Week 48); (2) who maintained the confirmed response < 50 copies/mL up to Week 48; (3) who did not achieve levels < 50 copies/mL or < 400 copies/mL by Week 48; (4) who had confirmed rebound (two consecutive values \geq 50 copies/mL after a confirmed response was seen); and (5) who were late responders ($>$ 1 log₁₀ drop only after Week 12, or first occurrence < 400 copies/mL only after Week 24). Absolute and change from baseline values for HIV-1 RNA and CD4 cell counts were summarized. The intent-to-treat (ITT) analysis set, which comprised the 100 subjects who took at least one dose of study drug and had no major protocol deviations, was used for efficacy assessments. Summary statistics were calculated for each efficacy endpoint (overall, for baseline HIV-1 RNA subgroups [\geq 100,000 and < 100,000 copies/mL], and for baseline CD4 values [\geq 200/ μ L and < 200/ μ L]).

Resistance Analysis: Baseline plasma samples from each subject were genotyped. Samples were collected and banked at all subsequent visits except Week 4. The HIV-1 reverse transcriptase (RT) and protease genes were sequenced and phenotypic analyses with TDF, FTC, and all US-FDA-approved RT inhibitors (RTIs) and PIs were performed on the last available sample if a subject met the following criteria: (1) did not achieve plasma HIV-1 RNA levels < 400 copies/mL by Week 24, confirmed within 4 weeks; (2) achieved plasma HIV-1 RNA levels < 400 copies/mL, and subsequently had two consecutive levels \geq 400 copies/mL, or had an unconfirmed rebound in plasma HIV-1 RNA levels \geq 400 copies/mL on study drug at Week 48; or (3) subjects who discontinued study drugs prior to Week 48 and had HIV-1 RNA levels \geq 400 copies/mL on their last on-treatment study visit.

STUDY SYNOPSIS (CONTINUED)

Statistical Methods (Continued):

Pharmacokinetics: Steady-state trough 24-hour plasma concentrations of FTC, tenofovir, ATV, and ritonavir were summarized at Weeks 4, 24, and 48 (or early study drug discontinuation). Concentrations were determined using a validated HPLC/MS/MS assay.

Adherence and Subject Satisfaction: Percent adherence was measured using pill counts across the entire study duration and by the subject questionnaire (1-week recall and 1-month recall). Reasons for missed medication doses were summarized. Responses on the subject questionnaire related to satisfaction with the treatment regimen were summarized.

Safety: Safety analyses included data from all 100 subjects who received at least one dose of study medication. All safety events that occurred after initiation of study drug and up to 30 days after discontinuation of the study drug were summarized. Clinical laboratory results and adverse events were coded using MedDRA, version 9; the Wilcoxon signed-rank test was performed to compare values at each time point with baseline values. Post-hoc analyses of parameters of interest were performed by baseline characteristic subgroup (e.g., changes in calculated creatinine clearance by race).

STUDY SYNOPSIS (CONTINUED)

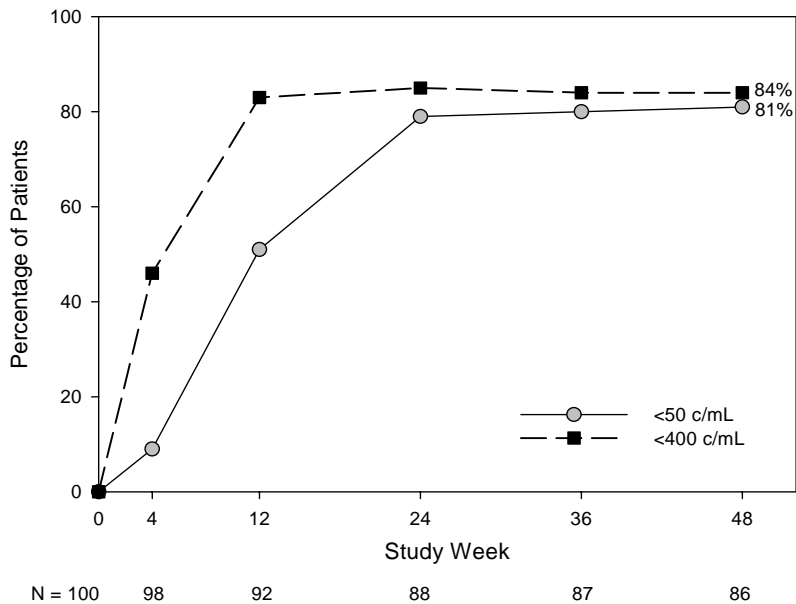
SUMMARY – RESULTS:

Disposition: Of the 100 treated subjects, 15 discontinued study medication early: six had safety/tolerability reasons, five were lost to follow-up, and four discontinued for other reasons.

Demographics: 82% male, 18% female; 58% White, 37% African-American, 1% American Indian or Alaska native, 4% Other; mean (SD) age: 39 (9.6) years.

Efficacy Results: Eighty-one percent of subjects (81/100) achieved HIV-1 RNA concentrations < 50 copies/mL at 48 weeks (79% at 24 weeks) (missing = failure). Fifty of 60 subjects (83%) with baseline HIV-1 RNA < 100,000 copies/mL and 31 of 40 subjects (78%) with baseline HIV-1 RNA \geq 100,000 copies/mL achieved HIV-1 RNA < 50 copies/mL at Week 48.

**Percentage of Subjects with HIV-1 RNA
Below 50 copies/mL or Below 400 copies/mL at Each Visit**



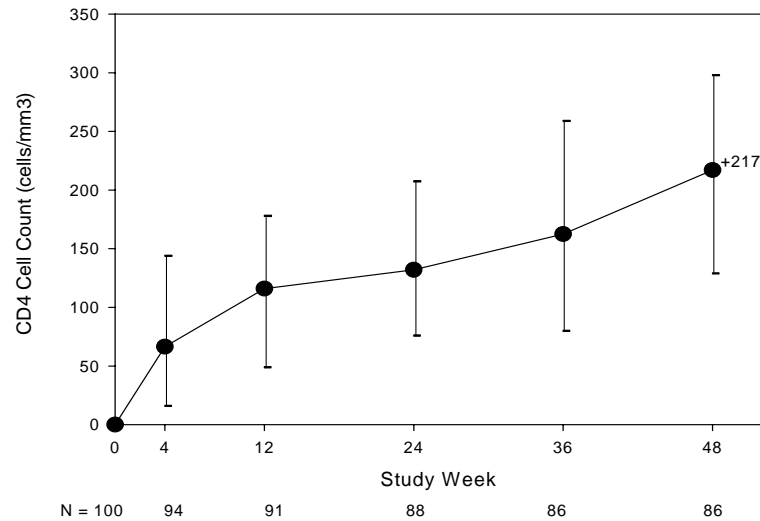
A total of 85% of subjects (85/100) had a confirmed response of HIV-1 RNA < 50 copies/mL during the study, and 82% (82/100) maintained a confirmed response < 50 copies/mL up to Week 48.

STUDY SYNOPSIS (CONTINUED)

Efficacy Results (Continued):

The median (interquartile range [IQR]) CD4 count increased from 256 (125–382) cells/ μ L at baseline to 385 (251–547) cells/ μ L at Week 24 and to 473 (304–605) cells/ μ L at Week 48. Overall, CD4 counts were significantly increased from baseline at each post-baseline visit ($p < 0.001$).

Median (IQR) CD4 Cell Count at Each Visit



Resistance Analysis Results: Baseline genotyping showed no detectable K65R, M184V, or primary PI-resistance mutations in any subject enrolled in the study. Thymidine-analogue mutations (specifically M41L, T215 reversions [T215D/E], and K219R) were detected in four subjects; these were not associated with reduced response to FTC/TDF + ATV/r. During the study period, resistance analysis was performed on banked samples from five subjects who met the resistance testing criteria, including two subjects who had HIV-1 RNA values ≥ 400 copies/mL at the time of early study drug discontinuation. One of these five subjects developed the M184V mutation selected by FTC. No other subjects developed the M184V mutation, any tenofovir-specific mutations (e.g. K65R), or any new PI mutations.

STUDY SYNOPSIS (CONTINUED)

Pharmacokinetics Results: At each measured time point (Weeks 4, 24, and 48), similar plasma trough concentrations were observed for each individual drug (FTC, tenofovir, ATV, and ritonavir).

**Plasma Trough Concentrations (ng/mL)
 Geometric Mean (90% Confidence Intervals)**

Analyte	Week 4	Week 24	Week 48
FTC	130.3 (108–157)	136.8 (109–171)	117 (93–147)
Tenofovir	71.6 (63–81)	82.3 (73–93)	81.4 (72–91)
ATV	613.6 (494–761)	608.7 (498–744)	641.8 (518–795)
Ritonavir	79.0 (60–103)	71.1 (56–90)	75.7 (56–102)

Adherence and Subject Satisfaction Results: At Week 48, 92% (72/78) of subjects self-reported full adherence (no doses missed) based on 1-week recall. Based on 1-month recall, 86% (69/80) of subjects reported \geq 95% adherence at Week 48. When adherence was assessed by pill counts, 84%, 86%, and 84% of subjects achieved \geq 95% adherence over 48 weeks for FTC/TDF, ATV, and ritonavir, respectively.

At Week 48, 90% (77/86) of subjects reported being “very satisfied” with their treatment regimen, 84% reported being “very satisfied” with the overall tolerability of treatment, 94% reported being “very satisfied” with the ability of the regimen to control HIV, and 86% reported being “very satisfied” with the simplicity and convenience of treatment. A majority of subjects (70%) reported that the general bothersome level with the treatment regimen’s side effects “does not bother me,” 26% reported that it “bothers me a little bit,” 1% reported that it “bothers me a lot,” and 3% reported that it “bothers me terribly.”

STUDY SYNOPSIS (CONTINUED)

Safety Results: The study regimen of FTC/TDF + ATV/r was generally safe and well tolerated. Treatment-emergent serious adverse events (SAEs) were experienced by 14% of subjects (14/100). Two deaths occurred during this study. One subject, a 46-year-old Caucasian male with a baseline CD4 count of 59 cells/ μ L, died due to multisystem organ failure as a consequence of colonic obstruction secondary to non-Hodgkin's lymphoma. The other death occurred in a 24-year-old African-American male with a baseline CD4 count of 3 cells/ μ L who developed a second occurrence of lactic acidosis after discontinuing from the study and consequently experienced cardiac arrest.

The most common adverse events ($\geq 10\%$ of subjects) were diarrhea (26%), nausea (19%), headache (14%), fatigue (13%), ocular icterus (13%), upper respiratory tract infection (13%), and vomiting (10%). Six subjects experienced treatment-emergent Grade 3 or 4 adverse events that were considered to be related to study drug (vomiting, hyperbilirubinemia [$n = 3$], hepatic enzyme increase, and lactic acidosis). Six subjects discontinued study drug early because of AEs (rash, hyperbilirubinemia, lactic acidosis, and hepatitis [treatment-related], and tuberculosis and increased creatinine [treatment-unrelated]).

Grade 3 and Grade 4 total bilirubin elevations occurred in 44% and 5% of subjects, respectively; however, these events were not associated with \geq Grade 3 increases in hepatic transaminase levels. One subject discontinued from the study early due to hyperbilirubinemia; this subject's total bilirubin increased from 1.1 mg/dL at baseline to 7.9 mg/dL by Week 12 (confirmed value). Direct bilirubin remained between 0.2 and 0.3 mg/dL throughout the study. After study drug was discontinued, total bilirubin returned to the normal range within 7 days.

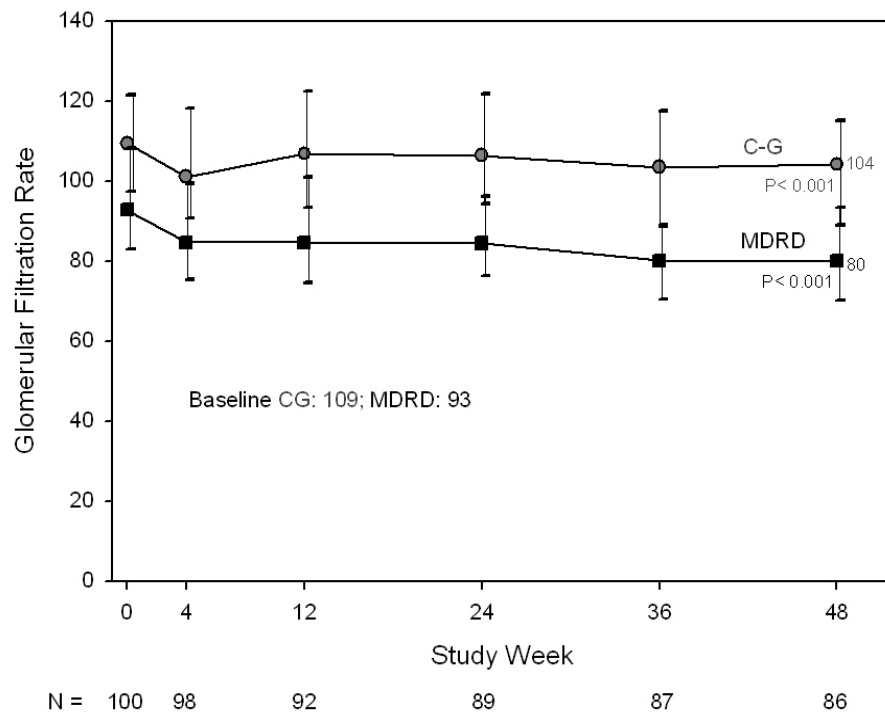
No cases of Fanconi syndrome or serious renal toxicity were seen, and no subjects experienced serum creatinine increases to greater than a Grade 2 level. Two subjects experienced confirmed Grade 1 or 2 serum creatinine increases.

STUDY SYNOPSIS (CONTINUED)

Safety Results (Continued):

Small reductions from baseline in estimated GFR were observed early but stabilized over 48 weeks (see figure below). In the overall safety population, median (IQR) change from baseline values were -7 ($-19, 2$) mL/min by the C-G method and -10 ($-20, -1$) mL/min/ 1.73 m^2 (GFR) by the MDRD method at Week 48.

Median (IQR) Estimated Glomerular Filtration Rate for Overall Safety Population at Each Study Visit (Estimated by C-G for Creatinine Clearance or MDRD)



Observed trends in estimated GFR by C-G were similar for African-American ($N = 37$) and non-African-American subjects ($N = 63$) through 48 weeks. At baseline, median (IQR) estimated GFR values were 106 ($93, 117$) mL/min for African-American subjects and 101 ($81, 112$) mL/min, for non-African-American subjects. The median change from baseline at 48 weeks was -8 ($-19, 2$) mL/min for African-Americans versus -7 ($-17, 2$) mL/min for non-African-Americans. Observed trends in estimated GFR by MDRD were also similar for African-American and non-African-American subjects through 48 weeks.

STUDY SYNOPSIS (CONTINUED)

Safety Results (Continued):

Median fasting total cholesterol (TC) and triglyceride (TG) values increased significantly from baseline to Week 48, with median change-from-baseline values of 11 and 5 mg/dL, respectively. At Week 48, median fasting HDL levels also were significantly increased from baseline (absolute 41 mg/dL, change 3 mg/dL), whereas median fasting LDL levels did not increase significantly from baseline. Overall, median LDL and TC at baseline and Week 48 were at or near the optimal (LDL < 100 or 100–129 mg/dL) and desirable (TC < 200 mg/dL) ranges as defined by the National Cholesterol Education Program, Adult Treatment Panel III. Over the course of the study, 5% of subjects took lipid-lowering agents and 6% took antidiabetes agents.

Fasting glucose, insulin, and C-peptide levels were measured at baseline, Week 24, and Week 48. Each of these parameters was shown to increase by Week 48; however, the degree of increase was not considered clinically significant.

Median (IQR) Metabolic Values

Parameter	Baseline Values	Change from Baseline Values	
		At Week 24	At Week 48
Fasting Lipid Profile (mg/dL)			
TC	152 (130, 187)	0 (-15, 18) p = 0.50	11 (-10, 24) p = 0.002
HDL	37 (29, 44)	2 (-2, 7.5) p = 0.006	3 (-2, 10) p < 0.001
TC/HDL	4.1 (3.6, 4.9)	-0.2 (-0.7, 0.2) p = 0.010	0.0 (-0.6, 0.4) p = 0.29
TG	113 (84, 148)	6 (-34, 30) p = 0.93	5 (-22, 47) p = 0.040
LDL	96 (75, 114)	-2.5 (-17, 15) p = 0.75	2.0 (-9, 18) p = 0.12
Other			
Fasting Glucose (mg/dL)	88 (83, 94)	3.0 (-3.5, 8.0) p = 0.026	2.0 (-3.0, 8.0) p = 0.047
Ultrasensitive Insulin (µIU/mL)	4.94 (3.38, 7.48)	0.46 (-1.71, 2.16) p = 0.30	0.27 (-1.43, 3.54) p = 0.11
C-Peptide (ng/mL)	1.86 (1.37, 2.53)	0.26 (-0.23, 0.79) p = 0.015	0.14 (-0.33, 0.87) p = 0.026

STUDY SYNOPSIS (CONTINUED)

CONCLUSIONS: Treatment with FTC/TDF in combination with ATV/r offers a simple treatment regimen that is safe, efficacious, and conducive to adherence. The regimen was well tolerated. FTC/TDF in combination with ATV/r demonstrated a favorable-to-neutral metabolic profile. This once-daily regimen provided effective suppression of plasma HIV-1 RNA levels and achieved a sustained immunologic response over 48 weeks in antiretroviral-naive subjects.