FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	Phase 3, Two-Part Study to Evaluate the Efficacy of Tenofovir Alafenamide versus Placebo Added to a Failing Regimen Followed by Treatment with Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide Plus Atazanavir in HIV-1 Positive, Antiretroviral Treatment-Experienced Adults
Name of Test Drug:	EVG/COBI/FTC/TAF [E/C/F/TAF])
Dose and Formulation:	Fixed-dose combination tablet of EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg
Indication:	HIV-1 Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-292-0117
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	111,007 2013-002830-19
ClinicalTrials.gov Identifier:	NCT01967940
Study Start Date:	25 October 2013 (First Subject Screened)
Study End Date:	31 July 2017 (Global Last Subject Last Visit)
Principal or Coordinating Investigator:	Name: Cissy Kityo, MBChB, MSc Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Hal Martin, MD, MPH Telephone: PPD Fax: PPD
Report Date:	14 May 2018

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-US-292-0117

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

Title of Study: A Phase 3, Two-Part Study to Evaluate the Efficacy of Tenofovir Alafenamide versus Placebo Added to a Failing Regimen Followed by Treatment with Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide Plus Atazanavir in HIV-1 Positive, Antiretroviral Treatment-Experienced Adults

Investigators: Multicenter.

Study Centers:

Part 1: Subjects were enrolled at a total of 17 sites: 2 sites in the Dominican Republic, 3 sites in the Russian Federation, 5 sites in Thailand, 1 site in Uganda, and 6 sites in the United States of America (USA).

Part 2: Subjects were enrolled at a total of 10 sites: 2 sites in the Dominican Republic, 2 sites in the Russian Federation, 3 sites in Thailand, 1 site in Uganda, and 2 sites in the USA.

Publications: There were no publications at the time of this CSR.

Study Period:

25 October 2013 (First Subject Screened)
31 July 2017 (Global Last Subject Last Visit)

Phase of Development: Phase 3

Objectives:

This study was conducted to evaluate the efficacy of tenofovir alafenamide (TAF) versus placebo as functional monotherapy for 10 days in subjects with nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) resistance failing their current HIV treatment regimen. This allowed assessment of the activity of the novel prodrug TAF against HIV-1 strains with NRTI mutations without the risk of accumulation of additional resistance mutations. Once functional monotherapy of the study was completed, a second open-label phase was designed to evaluate the safety and efficacy of a regimen containing elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/TAF (E/C/F/TAF; Genvoya®; hereafter referred to as "GEN") administered as a single fixed-dose combination (FDC) tablet plus atazanavir (ATV) in subjects failing their current regimen.

The primary objective of this study was as follows:

Part 1

- To evaluate the efficacy of TAF versus placebo, each administered with the existing, failing antiretroviral (ARV) regimen, as demonstrated by the proportion of subjects with HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ after 10 days of therapy in HIV-1 positive, ARV treatment-experienced adult subjects.

The secondary objectives of this study were as follows:

Part 1

- To evaluate the efficacy of TAF as demonstrated by the reduction in HIV-1 RNA at Day 10.

Part 2

- To evaluate the efficacy and safety of GEN plus ATV after 24 weeks of treatment in subjects switched from a failing regimen as determined by the achievement of plasma HIV-1 RNA < 50 copies/mL.
- To evaluate the efficacy and safety of GEN plus ATV after 48 weeks of treatment in subjects switched from a failing regimen.

Methodology: This was a partially-randomized, partially-blinded, multicenter, two part study.

Part 1

Part 1 consisted of 2 cohorts, starting with a Sentinel Cohort: 10 HIV-1 subjects were enrolled to receive open-label TAF 25 mg in addition to their current failing ARV regimen. This cohort was followed by a Randomized Cohort that was a double-blind, randomized comparison of the addition of TAF or placebo-to-match in HIV-1 positive adults failing their current ARV regimen. Randomization and dosing into the Randomized Cohort of Part 1 began after the Day 10 safety and efficacy data from the 10 subjects in the Sentinel Cohort had been reviewed.

In the Randomized Cohort, approximately 90 subjects failing their current ARV regimen were planned to be randomized 2:1 to TAF 25 mg versus placebo-to-match. These drugs were added to their current failing regimen for 10 days as follows:

- **Treatment arm 1:** Continue current failing regimen + TAF 25 mg once daily QD for 10 days (n = 60)
- **Treatment arm 2:** Continue current failing regimen + placebo-to-match once daily for 10 days (n = 30)

Part 2

Subjects who completed Day 10 of Part 1 (from either the Sentinel or Randomized Cohort) discontinued their TAF or placebo-to-match but remained on their failing ARV regimen until the site was notified of the subject's eligibility to proceed to Part 2.

Subjects who received TAF (including all subjects in the Sentinel Cohort and those on Treatment Arm 1 of the Randomized Cohort) and had a > 0.5 log_{10} decline in HIV-1 RNA began treatment with GEN plus ATV once daily for 48 weeks. Subjects on TAF (including all subjects in the Sentinel Cohort and those on Treatment Arm 1 of the Randomized Cohort) who had a ≤ 0.5 log_{10} decline in HIV-1 RNA were discontinued from the study and were not eligible to continue into Part 2 of the study. The Sponsor notified the site regarding subject enrollment criteria for Part 2 prior to the visit. All subjects in Treatment Arm 2 (placebo) in the Randomized Cohort were eligible to move into Part 2 regardless of their viral load change in Part 1.

An Independent Data Monitoring Committee (IDMC) reviewed the progress, efficacy, and safety data of this study while the study was ongoing. The committee convened after 25 subjects enrolled in Part 2 had completed Week 12 of the study.

Number of Subjects (Planned and Analyzed):

Planned: Sentinel Cohort: 10 subjects; Randomized Cohort: 90 subjects (60 in the TAF arm and 30 in the placebo arm).

Analyzed:
Part 1: 55 subjects (Safety and Full Analysis Sets [FAS]): 12 in Sentinel Cohort; 43 in Randomized Cohort (28 in the TAF arm, 15 in the placebo arm).

Part 2: 37 subjects (Safety and FAS).

Diagnosis and Main Criteria for Inclusion: Antiretroviral treatment-experienced HIV-1 positive adults ≥ 18 years of age of either sex, currently taking a failing ARV that contains tenofovir disoproxil fumarate (TDF), with plasma HIV-1 RNA levels ≥ 500 copies/mL but ≤ 100,000 copies/mL, documented primary resistance mutations to NRTIs by virtue of having a K65R mutation in reverse transcriptase (RT), and had an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 50 mL/min at screening.

Duration of Treatment: 10 days for Part 1(Sentinel Cohort and Randomized Cohort), followed by a period of no longer than 14 days to confirm eligibility to proceed to Part 2.

48 weeks for Part 2.

All subjects were offered to continue to receive GEN plus ATV after the completion of Part 2 until GEN became commercially available, or until Gilead Sciences terminated development of GEN in the applicable country.

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

Part 1: TAF 25 mg administered orally with food. Lot numbers CM1304D1, CM1404B1

Part 2: FDC tablet of GEN (E/C/F/TAF, 150/150/200/10 mg) plus ATV 300 mg administered orally once daily with food.

Lot numbers for GEN: CP1209B1, CP1307B1, CP1311B1, CP1313B1, CP1402B1, CP1403B1, CP1406B1, CP1503B1, CP1506B1, CP1603B1

Lot numbers for ATV: 3H64576, 4A84857, 3J76222A, 3K79431A, 4J79977, AAC2025

Reference Therapy, Dose, Mode of Administration, and Lot No.:

Part 1: Placebo-to-match tenofovir alafenamide 25 mg tablet administered once daily with food. Lot number: CM1206B1

Part 2: None

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ at Day 10 in Part 1.

Secondary efficacy endpoints:

Changes in plasma $\log_{10}$ HIV-1 RNA at Day 10 in Part 1, the percentage of subjects with HIV-1 RNA < 50 copies/mL and < 400 copies/mL at Week 24 and 48 as determined by the Food and Drug Administration (FDA)-defined snapshot algorithm, the change from baseline in plasma $\log_{10}$ HIV-1 RNA and CD4 cell counts and percentage at Week 24 and 48.

Pharmacokinetics: A pharmacokinetic (PK) study was performed in Part 1 and a PK substudy was performed during Part 2. As PK was not an endpoint of the study, PK data are not included in this clinical study report (CSR) but are reported separately in bioanalytical reports.

Safety: Adverse events (AEs) and clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy), and electrocardiograms (ECG). Renal safety was assessed with renal events and change from baseline at each visit for the following renal parameters: serum creatinine, $eGFR_{CG}$, eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) serum cystatin C method ($eGFR_{CKD\text{-}EPI}$ cystatin C) and eGFR using the CKD-EPI serum creatinine method ($eGFR_{CKD\text{-}EPI}$ creatinine), proteinuria by urinalysis and quantitative assessment (urine protein to creatinine ratio [UPCR], and tubular proteinuria (urine retinol binding protein [RBP] to creatinine ratio, urine beta-2-microglobulin to creatinine ratio).

Statistical Methods:

Efficacy: The FAS was the primary efficacy analysis set and included all subjects who (1) were enrolled into Part 1 of the study and (2) received at least one dose of study medication in Part 1. The analysis purpose of the primary efficacy endpoint was to assess the treatment effect of the TAF treatment relative to placebo. The null hypothesis was tested using the Fisher's exact test at significance level $\alpha = 0.05$. The difference in the proportion of subjects with plasma HIV-1 RNA decreases from baseline exceeding 0.5 log10 at Day 10 and the associated 2-sided 95% confidence interval was constructed using an unconditional exact method by inverting 1-sided tests.

For Part 2, the FAS includes all subjects who (1) were enrolled into Part 2 of the study and (2) received at least one dose of study medication in Part 2.

For the secondary endpoints, the changes from baseline in $\log_{10}$ HIV-1 RNA at Day 10 in Part 1 were summarized using descriptive statistics based on observed data (ie, missing = excluded [M = E]). The changes from baseline between treatment groups were compared with a two-sided Wilcoxon rank sum test at a significance level of 0.05. The difference and the associated 95% CI were constructed using Analysis of Variance (ANOVA models). All $\log_{10}$ HIV-1 RNA and CD4 were summarized using observed values (ie, M = E).

Pharmacokinetics: No PK analyses are included in this report.

Safety: Part 1 safety data were summarized for AEs, serious AEs (SAEs) and graded laboratory abnormalities. For Part 1 the subjects were grouped into 1 of 3 treatment groups: TAF in the sentinel cohort, TAF in the randomized cohort, and placebo in the randomized cohort. Part 2 safety data were summarized for AEs, SAEs, graded laboratory abnormalities, renal safety, vital signs and ECG. For Part 2, subjects were grouped to a single treatment group: GEN +ATV.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Summaries (number and percentage of subjects) of treatment-emergent AEs (by system organ class [SOC], high-level term, and preferred term [PT]) were provided by treatment. Treatment-emergent AEs were defined as those AEs with onset date on or after the study drug start date and no later than 30 days after the study drug stop date.

Summaries of laboratory data were provided for the safety analysis sets. Analyses were based on values reported in conventional units. Descriptive statistics were provided for each laboratory test. Graded laboratory abnormalities were defined using the Gilead Sciences Inc. grading for Severity of Adverse Events and Laboratory Abnormalities. The number and percentage of subjects in the safety analysis set with an investigator's ECG assessment of normal, abnormal but not clinically significant, or abnormal and clinically significant was summarized by baseline result for each visit.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

Enrollment into the study was stopped early due to the inability to recruit a sufficient number of subjects who met the eligibility criteria.

A total of 55 subjects were enrolled into Part 1 and received at least 1 dose of study drug: 12 in the Sentinel Cohort; 43 in the Randomized Cohort (28 in the TAF arm, 15 in the placebo arm). All subjects completed Part 1 of the study (Table 15.8.1.3).

A total of 38 subjects were enrolled in Part 2 of the study, and 37 subjects received at least 1 dose of GEN + ATV in Part 2. A total of 35 subjects (94.6%) completed Part 2. Reasons for discontinuation were AE (1 subject [2.7%]) and study terminated by the sponsor (1 subject [2.7%]) (Table 15.8.1.3). However, the sponsor did not terminate the study before Week 48 so the reason for discontinuation "study terminated by the sponsor" was an error on the Case Report Form. As the study site closed out in 2016, it is not possible to follow up on this subject.

Part 1:

Over half the subjects were male (32 out of 55 subjects, 58.2%). Median (range) age was 40 (22 to 55) years. Most subjects were Black (34 [61.8%]) or Asian (10 [18.2%]) and not Hispanic/Latino (49 [89.1%]). The median (Q1, Q3) baseline BMI was 24.3 (20.8, 28.1) kg/m^2. For the randomized cohort, demographic and baseline characteristics were generally similar between the 2 treatment groups (Table 15.8.3.1).

At baseline, the median (Q1, Q3) baseline HIV-1 RNA level was 4.13 (3.64, 4.69) log_{10} copies/mL and the majority of subjects had HIV-1 RNA ≤ 100,000 copies/mL (51 [92.7%]). Four subjects (7.3%) had HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL and no subjects had HIV-1 RNA > 400,000 copies/mL. The median (Q1, Q3) baseline CD4 count was 184 (109, 345) cells/μL. At baseline, 7 subjects (12.7%) had a CD4 cell count < 50 cells/μL, 24 subjects (43.6%) had counts of ≥ 50 to < 200 cells/μL, 8 subjects (14.5%) had counts of ≥ 200 to < 350 cells/μL, 11 subjects (20.0%) had counts of ≥ 350 to < 500 cells/μL, and 5 subjects (9.1%) had counts ≥ 500 cells/μL. The most common risk factor for HIV infection was heterosexual sex (46 subjects [83.6%]). Twenty five subjects (45.5%) were asymptomatic, 13 (23.6%) were symptomatic, and 17 (30.9%) had acquired immunodeficiency syndrome (AIDS) as defined by the Centers for Disease Control and Prevention (CDC) guidelines. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 100.3 (80.7, 129.7) mL/min. For the randomized cohort, baseline disease characteristics were generally similar between the 2 treatment groups (Table 15.8.3.3).

Part 2:

The majority of subjects were male (22 out of 37 subjects, 59.5%). Median (range) age was 41 (22 to 55) years. The majority of subjects were Black (20 [54.1%]) or Asian (8 [21.6%] and not Hispanic/Latino (32 [86.5%]). The median (Q1, Q3) baseline BMI was 23.6 (20.8, 28.6) kg/m^2 (Table 15.8.3.2).

At baseline, the median (Q1, Q3) baseline HIV-1 RNA level was 4.49 (4.20, 4.66) log_{10} copies/mL and the majority of subjects (33 [89.2%]) had HIV-1 RNA ≤100,000 copies/mL. Three subjects (8.1%) had HIV-1 RNA > 100,000 copies/mL and ≤ 400,000 copies/ml, and no subjects had HIV-1 RNA > 400,000 copies/mL. The median (Q1, Q3) baseline CD4 count was 180 (115, 312) cells/μL. At baseline, 0 subjects had a CD4 cell count < 50 cells/μL, 21 (56.8%) had counts of ≥ 50 to < 200 cells/μL, and 5 (13.5%) had counts of ≥ 200 to < 350 cells/μL, 7 (18.9%) had counts ≥ 350 to < 500 cells/μL, and 3 (8.1%) had counts ≥ 500 cells/μL. The most common risk factor for HIV infection was heterosexual sex

(29 subjects [78.4%]). Eighteen subjects (48.6%) were asymptomatic, 9 (24.3%) were symptomatic, and 10 (27.0%) had AIDS as defined by the CDC guidelines. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 108.4 (84.7, 131.2) mL/min (Table 15.8.3.4).

For Part 1 and Part 2, medical history data are listed by subject in Listing 16.2.4.4 and nonstudy drug ARV medications in Listing 16.2.4.6. Concomitant non-ARV medications are listed in Listing 16.2.4.7.1 and Listing 16.2.4.7.2, for Part 1 and Part 2, respectively.

Efficacy Results:

Part 1:

Sentinel Cohort:

The proportion of subjects with decreases in plasma HIV-1 RNA > 0.5 log_{10} at Day 10 was 7 out of 12 subjects (58.3%) (Table 15.9.2.1).

HIV-1 RNA decreased from baseline to Day 10. Mean (SD) baseline value was 4.18 (0.648) log_{10} copies/mL. The mean (SD) change from baseline in HIV-1 RNA at Day 10 was -0.72 (0.574) log_{10} copies/mL (Table 15.9.2.3).

CD4 cell counts increased from baseline to Day 10. Mean (SD) baseline CD4 cell counts were 269 (207.1) cells/μL. Mean (SD) change from baseline at Day 10 was 26 (99.3) cells/μL (Table 15.9.2.5). Mean (SD) baseline CD4 % was 17.4% (10.14%). Mean (SD) change from baseline at Day 10 was 0.9% (5.35%) (Table 15.9.2.7).

Randomized Cohort:

The proportion of subjects with decreases in plasma HIV-1 RNA > 0.5 log_{10} at Day 10 was 17 out of 28 subjects (60.7%) and 0 out of 15 subjects (0%) for the TAF and placebo groups, respectively (proportional difference 60.7% [95% CIs: 42.6% to 78.8%]; $p < 0.001$). (Table 15.9.2.1).

HIV-1 RNA decreased from baseline to Day 10 for the TAF group but changes in the placebo group were minimal (Table 15.9.2.3). Mean (SD) baseline value was 4.16 (0.544) log_{10} copies/mL and 4.03 (0.953) log_{10} copies/mL for the TAF and placebo groups, respectively. The mean (SD) change from baseline in HIV-1 RNA at Day 10 was -0.70 (0.628) log_{10} copies/mL and -0.04 (0.233) log_{10} copies/mL (difference in least square mean [LSM] -0.66 log_{10} copies/mL [95% CIs: -1.00, -0.32 log_{10} copies/mL]; $p < 0.001$).

Mean (SD) baseline CD4 cell counts were 245 (244.6) cells/μL and 232 (162.4) cells/μL for the TAF and placebo groups, respectively. Mean (SD) change from baseline at Day 10 was 19 (82.2) cells/μL and -6 (49.6) cells/μL, respectively (difference in LSM: 28 cells/μL [95% CIs: -21, 77 cells/μL]; $p = 0.25$) (Table 15.9.2.5). Mean (SD) baseline CD4 % was 16.5% (11.09%) and 14.3% (8.61%) for the TAF and placebo groups, respectively. Mean (SD) change from baseline at Day 10 was 0.0% (2.56%) and 0.2% (2.13%), respectively (difference in LSM: -0.2% [95% CIs: -1.9, 1.4%]; $p = 0.78$) (Table 15.9.2.7).

Part 2:

The majority of patients had HIV-1 RNA < 50 copies/mL by Week 4 (26 out of 37 subjects [70.3%], M = E). High rates of viral suppression were maintained throughout the study

(Figure 15.9.2.1, Table 15.9.2.2).

HIV-1 RNA values decreased from baseline throughout the study, with the fastest decreases from baseline observed during the first 4 weeks (Figure 15.9.2.2, Table 15.9.2.4). Mean (SD) baseline HIV-1 RNA value was 4.34 (0.600) $\log_{10}$ copies/mL. The mean (SD) change from baseline at Week 24 (N = 35) was -2.96 (0.754) $\log_{10}$ copies/mL. The mean (SD) change from baseline at Week 48 (N = 35) was -3.04 (0.594) $\log_{10}$ copies/mL.

CD4 cell count generally increased throughout the study (Figure 15.9.2.3, Table 15.9.2.6). Mean (SD) CD4 cell count at baseline was 251 (203.3) cells/μL. Mean (SD) change from baseline to Week 24 (N = 35) was 76 (92.8) cells/μL. Mean (SD) change from baseline to Week 48 (N = 35) was 125 (109.0) cells/μL.

Mean (SD) CD4 % at baseline was 15.6% (8.51%). Mean (SD) change from baseline to Week 24 (N = 35) was 4.4% (2.35%). Mean (SD) change from baseline to Week 48 (N = 35) was 5.7 (2.99) cells/μL (Table 15.9.2.8).

The percentage of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 24 using the US FDA-defined snapshot algorithm was 32 (86.5%). Four subjects (10.8%) had HIV-1 RNA ≥ 50 copies/mL and 1 subject (2.7%) had no virologic data in the Week 24 window (discontinued the study due to an AE) (Table 15.9.2.9.1). Using a cut-off of HIV-1 RNA of 400 copies/mL, 35 subjects (94.6%) had HIV-1 RNA < 400 copies/mL at Week 24. One subject (2.7%) had HIV-1 RNA ≥ 400 copies/mL and 1 subject (2.7%) had no virologic data in the Week 24 window (discontinued the study due to an AE) (Table 15.9.2.9.2).

The percentage of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA defined snapshot algorithm was 36 (97.3%). One subject (2.7%) had no virologic data in the Week 48 window (discontinued the study due to an AE) (Table 15.9.2.9.3). The same results were obtained when using a cut-off of HIV-1 RNA of 400 copies/mL (Table 15.9.2.9.4).

Pharmacokinetics: No PK analyses are included in this CSR but are reported separately in bioanalytical reports.

Safety Results:

Part 1:

Sentinel Cohort:

Adverse Events:

Seven out of 12 subjects (58.3%) had a least 1 treatment-emergent AE (Table 15.11.2.1.1.1). All subjects had Grade 1 or 2 AEs (Listing 16.2.7.1.1). No subjects died, experienced SAEs, or experienced AEs leading to discontinuation of study drug. No subjects had any Center for Disease Control (CDC) Class C AIDS defining events (Listing 16.2.7.3). Nausea was the only AE experienced by 2 subjects (16.7%); all other AEs were experienced by < 2 subjects (Table 15.11.2.1.2.1). Two subjects (16.7%) experienced AEs that were considered related to the study drug by the investigator: nausea and insomnia (1 subject) and nausea and dizziness (1 subject) (Listing 16.2.7.1.1).

Laboratory Data:

Five subjects (41.7%) experienced treatment-emergent laboratory abnormalities. All were

Grade 1 except for a Grade 3 abnormality of neutrophils decreased (Table 15.11.6.4.1 and Table 15.11.6.4.5).

Other Safety Data:

There were no pregnancies (Listing 16.2.8.5).

Randomized Cohort:

Adverse Events:

The percentages of subjects with at least 1 treatment-emergent AEs were as follows: TAF 13 subjects (46.4%); placebo 5 subjects (33.3%). The majority of subjects had Grade 1 or Grade 2 AEs; 3 subjects (10.7%) in the TAF group and 0 subjects in the placebo group experienced Grade 3 AEs (Table 15.11.2.1.1.1). No subjects experienced Grade 4 events. Three subjects (10.7%) in the TAF group experienced SAEs (hypoglycemia, myopathy, and spontaneous abortion [Table 15.11.4.1.1.1]); none of the SAEs were considered related to study drug. No subjects in the placebo group experienced SAEs. No subjects in either treatment group died or experienced AEs leading to discontinuation of study drug (Table 15.11.2.1.1.1). One subject in the placebo group experienced a CDC Class C AIDS defining event of disseminated tuberculosis (Listing 16.2.7.3). No AE was experienced by > 1 subject in either treatment group (Table 15.11.2.1.2.1). Two subjects (7.1%) in the TAF group experienced AEs that were considered related to the study drug by the investigator: nausea (1 subject) and jaundice (1 subject). No subjects in the placebo group experienced AEs that were considered related to study drug (Listing 16.2.7.1.1).

Full subject narratives for subjects experiencing SAEs are included in Section 15.2.

Laboratory Data:

Fifteen subjects (53.6%) in the TAF group experienced treatment-emergent laboratory abnormalities. The majority were Grade 1 or 2 abnormalities. One subject experienced a treatment-emergent Grade 3 abnormality of amylase increased. This subject had Grade 2 amylase increased at baseline. One subject experienced a Grade 4 abnormality of alanine aminotransferase (ALT) increased, a Grade 4 abnormality of gamma glutamyltransferase (GGT) increased, and a Grade 3 abnormality of total bilirubin increased (Table 15.11.6.4.1 and Table 15.11.6.4.5). This subject had abnormal Grade 3 ALT, Grade 4 aspartate aminotransferase and Grade 2 GGT at baseline (Listing 16.2.8.1.8.1) but no medical history of liver disease or hepatitis (Listing 16.2.4.4 and Listing 16.2.8.1.5). The subject's concomitant failing treatment regimen contained lamivudine (3TC), nevirapine (NVP), and ATV (Listing 16.2.4.6) which are associated with liver function test abnormalities. These abnormalities improved when the subject switched to GEN + ATV in Part 2 of the study (Listing 16.2.8.1.2.8). Six subjects (40.0%) in the placebo group experienced treatment-emergent laboratory abnormalities. All were Grade 1 or Grade 2 (Table 15.11.6.4.1).

Other Safety Data:

One subject in the TAF group became pregnant during the study (Listing 16.2.8.5). Her last dose of study drug was on Day 10. On Day 25 it was confirmed that the subject was pregnant. On Day 39, the subject experienced a spontaneous abortion which was reported as an SAE. A full subject narrative is included in Section 15.2.

Part 2:

Exposure to Study Drug:

The median (Q1, Q3) duration of exposure to GEN + ATV was 72.0 (60.9, 117.4) weeks. Thirty-six subjects (97.3% received study drug for ≥ 48 weeks and 22 (59.5%) received study drug for ≥ 72 weeks (Table 15.11.1.1).

Adverse Events:

Thirty subjects (81.1%) had at least 1 treatment-emergent AE. Most subjects had Grade 1 or Grade 2 AEs; 7 subjects (18.9%) had Grade 3 or 4 AEs (Table 15.11.2.1.1.2 and Table 15.11.2.2.2.1). Four subjects (10.8%) experienced SAEs (enlarged uvula, hyperbilirubinaemia, angioedema, and hypotension (Table 15.11.4.1.1.2). Only the SAE of hyperbilirubinaemia was considered related to study drug (Table 15.11.4.1.2). This SAE also led to premature discontinuation of study drug (Table 15.11.5 and Listing 16.2.7.9). No subjects died during the study (Table 15.11.2.1.1.2) and no subjects had any CDC Class C AIDS defining events (Listing 16.2.7.3). The most common AEs (ie, AEs that occurred in ≥ 10% of subjects) were: upper respiratory tract infection (11 subjects [29.7%]), malaria (5 subjects [13.5%]), headache (4 subjects [10.8%]), and hyperbilirubinaemia (4 subjects [10.8%]) (Table 15.11.2.1.2.4). Six subjects (16.2%) experienced AEs that were considered related to the study drug by the investigator: glomerular filtration rate decreased, chronic kidney disease, dizziness, proteinuria, and hyperbilirubinaemia (1 subject each), and jaundice and hyperbilirubinaemia (1 subject) (Listing 16.2.7.1.2).

Full subject narratives for subjects experiencing SAEs or AEs leading to discontinuation of study drug are included in Section 15.2.

Renal Safety:

No subjects had an AE of proximal renal tubulopathy (Table 15.11.2.1.2.4) or discontinued study drugs due to a renal AE (Table 15.11.5).

Three subjects had non-serious renal AEs considered related to study drug by the investigator (Table 15.11.2.3.1.1). In 2 subjects, the renal AEs (glomerular filtration rate decreased in 1 subject and proteinuria in the other) resolved with study drug continuation. One subject with a decreased creatinine clearance at baseline and a history of hypertension, had a Grade 1 serum creatinine abnormality (Table 15.11.6.4.2) and experienced an AE of chronic kidney disease. The subject started unspecified herbal medicines prior to the Grade 1 serum creatinine abnormality, which resolved after discontinuation of the herbal medicine, losartan, and metformin, while the study drugs were continued.

Changes from baseline in $eGFR_{CG}$ and $eGFR_{CKD-EPI}$ were minimal throughout the study (Table 15.11.6.2.25 and Table 15.11.6.2.26).

At baseline, the median (Q1, Q3) urine RBP to creatinine ratio was 86.0 (58.6, 127.4) µg/g. Median (Q1, Q3) percent change from baseline at Week 24 and Week 48 was 19.7% (-30.1%, 41.5%) and 21.9% (-20.1%, 72.3%), respectively (Table 15.11.2.4.4.1).

At baseline, the median (Q1, Q3) urine beta-2-microglobin to creatinine ratio was 145.8 (88.0, 231.0) µg/g. Median (Q1, Q3) percent change from baseline at Week 24 and

Week 48 was -39.8% (-55.6%, 6.1%) and -33.6% (-57.1%, -0.9%), respectively (Table 15.11.2.4.4.2).

At baseline, the median (Q1, Q3) UPCR was 6.95 (4.61, 11.25) mg/g. Median (Q1, Q3) percent change from baseline at Week 24 and Week 48 was -18.61% (-48.07%, 19.59%) and -12.56% (-33.77%, 38.78%), respectively (Table 15.11.2.4.4.3).

At baseline, median (Q1, Q3) urine creatinine was 116.0 (92.0, 212.0) mg/dL. Median (Q1, Q3) percent change from baseline at Week 24 and Week 48 was -4.7% (-44.1%, 48.1%) and -18.6% (-48.7%, 91.9%), respectively (Table 15.11.2.4.4.4).

Laboratory Data:

There were no clinically relevant changes from baseline in median values for haematology (Table 15.11.6.1.1 to Table 15.11.6.1.13) or clinical chemistry parameters (Table 15.11.6.2.1 to Table 15.11.6.2.26) and median values were generally within the reference ranges (Listing 16.2.8.1.10). There were increases from baseline in total bilirubin (Table 15.11.6.2.13) but this is expected given the known effects of ATV.

Thirty-six subjects (97.3%) experienced treatment-emergent laboratory abnormalities (Table 15.11.6.4.2). Twenty subjects (54.1%) experienced Grade 3 or 4 treatment-emergent laboratory abnormalities (Table 15.11.6.4.6). The most common Grade 3 abnormalities were total bilirubin increased (8 subjects [21.6%]) and hematuria (6 female subjects [16.2%]). Three subjects (8.1%) experienced Grade 4 treatment-emergent laboratory abnormalities: neutrophils decreased and total bilirubin increased (1 subject); creatine kinase increased (1 subject); total bilirubin increased (1 subject) Listing 16.2.8.1.8.2).

Vital Signs, Electrocardiogram, and Other Safety Data:

There were no clinically relevant changes in blood pressure (Table 15.11.7.1.1 and Table 15.11.7.1.2), pulse (Table 15.11.7.1.3), respiration rate (Table 15.11.7.1.4), temperature (Table 15.11.7.1.5), or body weight (Table 15.11.7.2).

Of the 25 subjects with normal ECGs at baseline, 18 remained normal at Week 48 and 7 had a non-clinically significant abnormality. Of the 12 subjects with a non-clinically significant abnormality at baseline, 9 remained abnormal (non-clinically significant), 2 were normal, and data were missing for 1 subject (Table 15.11.8).

A total of 34 out of 37 (91.9%) received concomitant non-ARV medications during the study. The most common medications (taken by ≥ 20% of subjects) were bactrim (21 subjects [56.8%]), paracetamol (14 subjects [37.8%]), spektramox (11 subjects [29.7%]), and diclofenac (10 subjects [27.0%]) (Table 15.11.7.3).

There were no pregnancies in Part 2 of the study (Listing 16.2.8.5).

CONCLUSIONS:

- At Day 10, 58.3% of subjects had decreases in plasma HIV-1 RNA > 0.5 $\log_{10}$.
- GEN+ATV resulted in high rates of HIV virologic suppression in subjects switching from a failing ARV regimen containing TDF. This was maintained throughout the study.

- Increased CD4 cell counts and CD4 percentage were maintained throughout the study.
- GEN+ATV was generally safe and well tolerated, with no on study deaths and low incidences of SAEs, discontinuations of study drug due to AEs, and Grade 3 or 4 AEs.
- No subjects had an AE of proximal renal tubulopathy or discontinued study drugs due to a renal AE