FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single Tablet Regimen Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen in HIV-1 Infected, Antiretroviral Treatment-Naive Adults
Name of Test Drug:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (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:	Human immunodeficiency virus type 1 (HIV-1) infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-292-0102
Phase of Development:	Phase 2
IND No.: **EudraCT No.:**	111,007 Not Applicable
ClinicalTrials.gov Identifier:	NCT 01497899
Study Start Date:	28 December 2011 (First Subject Screened)
Study End Date:	22 August 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Paul Edward Sax, MD Affiliation: PPD
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Report Date:	10 April 2017
Previous Report Date(s):	28 July 2014 (Week 96 Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-292-0102
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single Tablet Regimen Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen in HIV-1 Infected, Antiretroviral Treatment-Naive Adults

Investigators: Multicenter

Study Centers: Subjects were enrolled at a total of 41 study sites: 40 in the United States of America (USA) and 1 in Puerto Rico.

Publications: Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, Wang H, Callebaut C, Martin H, Fordyce MW, McCallister S. Tenofovir Alafenamide vs. Tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr. 2014; 67(1): 52-8.

Study Period:

28 December 2011 (First Subject Screened)
22 August 2016 (Last Subject Last Observation)

Phase of Development: Phase 2

Objectives:

This study was conducted to assess the safety and efficacy of a regimen containing elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (E/C/F/TAF; Genvoya®; hereafter referred to as "GEN") administered as a single fixed-dose combination (FDC) tablet versus E/C/F/tenofovir disoproxil fumarate (TDF) (Stribild®; STB) administered as an FDC tablet in HIV-infected, antiretroviral therapy (ART)-naive adult subjects. The study also included an open-label (OL) extension phase of GEN in ART-naive subjects and virologically suppressed subjects switching treatment to GEN from either STB or a COBI-boosted darunavir (DRV; D)-containing regimen (DRV+COBI).

The primary objective of this study was as follows:

- To evaluate the efficacy of a regimen containing E/C/F/TAF versus E/C/F/TDF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 24.

The secondary objectives of this study were as follows:

- To evaluate the efficacy of a regimen containing E/C/F/TAF versus E/C/F/TDF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48.
- To evaluate the safety and tolerability of the 2 treatment regimens through 48 weeks of treatment.
- To evaluate the safety and efficacy of switching subjects suppressed on a regimen containing DRV+COBI to GEN.

The primary objective and the first 2 secondary objectives described above were addressed in the Week 96 interim clinical study report (CSR), and are not addressed further in this report. The third secondary objective is addressed in this final report and includes data analysis from all subjects who have either completed the OL extension phase or prematurely discontinued from the study.

The designations EVG/FTC/COBI/TAF and E/C/F/TAF are used in preprogrammed tables, figures, and listings and to describe the All GEN Analysis Set.

Methodology: This was a multicenter study conducted in 2 phases: a randomized, double-blind, active-controlled phase and an OL extension phase. Subjects were randomized in a 2:1 ratio to 1 of the following 2 treatment groups:

Treatment Group 1: FDC tablet of GEN (E/C/F/TAF, 150/150/200/10 mg) + placebo-to-match STB once daily (n = 100)

Treatment Group 2: FDC tablet of STB (E/C/F/TDF, 150/150/200/300 mg) + placebo-to-match GEN once daily (n = 50)

Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

After Week 48, subjects continued to take their blinded study drug and attend visits every 12 weeks until treatment assignments were unblinded. Unblinding of the study drug took place after all subjects completed their Week 48 visit and the database freeze had occurred, at which point all subjects returned for an unblinding visit. At the unblinding visit, subjects were given the option to receive GEN in an OL extension phase until it became commercially available.

HIV-infected subjects who were actively participating in Gilead Sciences-sponsored Study GS-US-299-0102 were also eligible to participate in the OL extension phase and received GEN in this study until it became commercially available. Subjects randomized in Study GS-US-299-0102 received either D/C/F/TAF plus placebo-to-match DRV and COBI tablets and FTC/TDF (Truvada®; TVD) or DRV+COBI+TVD plus placebo-to-match D/C/F/TAF.

Subjects who declined participation in the OL extension phase, as well as those who completed the OL extension phase, returned to the clinic 30 days after the completion of study drugs for a 30-Day Follow-Up Visit.

Number of Subjects (Planned and Analyzed):
Planned: 150 subjects in the double-blind phase (100 subjects in the GEN group and 50 subjects in the STB group).

Approximately 300 subjects (including those from the double-blind phase and from Study GS-US-299-0102) could enter the OL extension phase.

Analyzed in the all GEN analysis (by analysis set):

	GEN	STB to GEN	D/C/F/TAF to GEN	DRV+COBI+TVD to GEN	All TDF to GEN
Subjects in All GEN Analysis Set	112	53	70	38	91
Subjects in All GEN Hip DXA Analysis Set	103 (92.0%)	52 (98.1%)	68 (97.1%)	36 (94.7%)	88 (96.7%)
Subjects in All GEN Spine DXA Analysis Set	106 (94.6%)	53 (100.0%)	69 (98.6%)	37 (97.4%)	90 (98.9%)

The denominator for percentages is based on the number of subjects in the All GEN Analysis Set.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in the double-blind phase of the study were HIV-infected adults with plasma HIV-1 RNA levels ≥ 5000 copies/mL, no prior use of any approved or experimental anti-HIV drug for any length of time, and had an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 70 mL/min at screening.

Additional subjects enrolled into the OL extension phase had received a DRV + COBI containing regimen in Study GS-US-299-0102, were treatment naive at the time of entry into that study, had reached at least the Week 48 visit (protocol-defined secondary endpoint), and were virologically suppressed (HIV-1 RNA < 50 copies/mL at the last study visit). These subjects were required to have an $eGFR_{CG}$ > 50 mL/min at entry into this study.

All subjects had documented sensitivity to TDF and FTC and CD4 cell count > 50 cells/μL.

Duration of Treatment: Subjects were treated for 48 weeks in the randomized, double-blinded phase. After Week 48, subjects continued to take their blinded study drug until treatment assignments were unblinded, at which point all subjects were given the option to receive GEN in the OL extension phase until it became commercially available. Subjects who declined participation in the OL extension phase, as well as those who completed the OL extension, returned to the clinic 30 days after the completion of study drugs for a 30-Day Follow-Up Visit.

Test Product, Dose, Mode of Administration, and Batch No.: FDC tablet of GEN (E/C/F/TAF, 150/150/200/10 mg) administered orally once daily with food.

Lot numbers for the OL extension phase: CP1208B1, CP1305B1, CP1311B1, CP1313B1, CP1401B1, CP1403B1, CP1314B1, and CP1504B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: Not applicable for the OL extension phase of the study.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 as determined by the Food and Drug Administration (FDA)-defined snapshot algorithm (presented in the interim Week 96 CSR).

Secondary efficacy endpoints for the final analysis included HIV-1 RNA levels, CD4 cell counts and CD4%, and resistance testing.

Pharmacokinetics: Pharmacokinetic (PK) parameters were not evaluated for switch groups during the OL extension phase. All PK data were presented in the interim Week 96 CSR.

Safety: Adverse events (AEs) and clinical laboratory tests, including bone mineral density (BMD) using dual energy x-ray absorptiometry (DXA), bone biomarkers (eg, C-type collagen sequence [CTx] and procollagen type 1 N-terminal propeptide [P1NP]), serum creatinine, eGFR by 2 formulae ($eGFR_{CG}$ and eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [$eGFR_{CKD\text{-}EPI,\ creatinine}$]), and renal biomarkers (eg, urine retinol-binding protein [RBP], beta-2-microglobulin, urine protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR], renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate [TmP/GFR], fractional excretion of phosphate [$FEPO_4$], and fractional excretion of uric acid [FEUA]) were performed to evaluate the safety and tolerability of GEN in the OL extension phase.

Statistical Methods:

Efficacy: The All GEN Analysis Set included all subjects who received at least 1 dose of double-blinded GEN during the double-blind phase and those subjects who received OL GEN during the OL extension phase. This was the Primary Analysis Set for all GEN efficacy analyses.

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL using the Missing = Excluded (M = E) method for imputing missing HIV-1 RNA values, and changes in CD4 cell count and CD4% based on observed, on-treatment data were summarized by visit using descriptive statistics for the All GEN Analysis Set.

Pharmacokinetics: No PK assessments were performed for this report. All PK data were presented in the interim Week 96 CSR.

Safety: Safety data were summarized for all subjects in the All GEN Analysis Set by treatment group using descriptive statistics as assigned during the OL extension phase and overall, unless specified otherwise.

The baseline value was defined based on Study Day 1 for the OL extension phase for subjects who switched to GEN from STB or who entered the OL extension phase of this study from Study GS-US-299-0102. For all other subjects, baseline value was based on Study Day 1 of the randomized phase of Study GS-US-292-0102.

Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 19.0.

All safety data collected during the study were listed (Appendix 16.2).

SUMMARY OF RESULTS:

Subject Disposition: A total of 171 subjects were randomized and 170 randomized subjects received at least 1 dose of study drug in the double-blind phase of the study (GEN 112 subjects; STB 58 subjects); 1 subject randomized to GEN did not receive study drug. Of the subjects who received at least 1 dose of study drug in the double-blind phase of the study, 105 of 112 subjects in the GEN group entered the OL extension phase and continued to receive GEN. Of the 58 subjects who received STB in the double-blind phase, 53 switched to receive OL GEN in the extension phase. From Study GS-US-299-0102, 70 subjects who received D/C/F/TAF and 38 subjects who received DRV+COBI+TVD in that study switched to receive OL GEN in the extension phase of this study.

For this final analysis, data for 273 subjects who received blinded and/or OL GEN in the following 3 groups are presented: GEN (112 subjects), D/C/F/TAF to GEN (70 subjects), and All TDF (STB or DRV+COBI+TVD) to GEN (91 subjects).

Subjects who discontinued GEN during the double-blind or OL extension phase were as follows: GEN 23.2%, 26 subjects; D/C/F/TAF to GEN 12.9%, 9 subjects; All TDF to GEN 13.2%, 12 subjects. The most common reason for the discontinuation of GEN was lost to follow up (GEN 9.8%, 11 subjects; D/C/F/TAF to GEN 7.1%, 5 subjects; All TDF to GEN 8.8%, 8 subjects) (Section 15.1, Table 2).

Subject Demographics and Baseline Disease Characteristics:

Demographic and general baseline characteristics were as expected for the populations studied.

Overall, the majority of subjects were male (GEN 96.4%; D/C/F/TAF to GEN 95.7%; All TDF to GEN 95.6%), with a mean age at the first GEN dose as follows: GEN 35 years (range 18 to 71 years); D/C/F/TAF to GEN 36 years (range 22 to 69 years); All TDF to GEN 37 years (range 20 to 59 years). Most subjects were white (GEN 66.1%; D/C/F/TAF to GEN 70.0%; All TDF to GEN 65.9%) and not Hispanic or Latino (GEN 77.7%; D/C/F/TAF to GEN 71.4%; All TDF to GEN 80.2%). The mean (SD) baseline values for body mass index at the first GEN dose were as follows: GEN 26.0 (4.31) kg/m^2; D/C/F/TAF to GEN 27.7 (5.75) kg/m^2; All TDF to GEN 26.0 (4.70) kg/m^2 (Section 15.1, Table 4).

In the GEN group, all subjects had baseline ≥ 1000 copies/mL HIV-1 RNA. The mean (SD) baseline CD4 cell count was 404 (181.6) cells/μL. The most common HIV risk factor category was homosexual sex (89.3%). Most subjects had no proteinuria (Grade 0 by dipstick) on urinalysis (90.2%). The mean (SD) $eGFR_{CG}$ value was 120.4 (30.77) mL/min.

In the switch groups, most subjects had HIV-1 RNA < 50 copies/mL at the OL extension phase baseline (D/C/F/TAF to GEN 97.1%; All TDF to GEN 93.4%). The mean (SD) baseline CD4 counts were as follows: D/C/F/TAF to GEN 631 (213.2) cells/μL; All TDF to GEN 654 (282.3) cells/μL. The most common HIV risk factor category was homosexual sex (D/C/F/TAF to GEN 87.1%; All TDF to GEN 89.0%). Most subjects had no proteinuria (Grade 0 by dipstick) on urinalysis (D/C/F/TAF to GEN 91.4%; All TDF to GEN 96.7%). The mean (SD) $eGFR_{CG}$ values for the switch groups were as follows: D/C/F/TAF to GEN 114.6 (32.44) mL/min; All TDF to GEN 102.9 (22.15) mL/min (Section 15.1, Table 5).

Efficacy Results:

Consistent with the data reported in the Week 96 CSR, high rates of virologic suppression were achieved and maintained through 192 weeks of treatment with GEN in treatment naive subjects. High rates of virologic suppression were also maintained for subjects who switched to receive GEN in the OL extension phase. The percentages of subjects with HIV-1 RNA < 50 copies/mL (missing = excluded [M = E] method) at selected time points were as follows: Week 192 GEN 97.8% (91 of 93 subjects); Week 108 D/C/F/TAF to GEN 98.5% (64 of 65 subjects); Week 108 All TDF to GEN 97.5% (79 of 81 subjects) (Section 15.1, Table 9).

Consistent with the data reported in the Week 96 CSR, CD4 cell counts increased from baseline through 192 weeks of treatment with GEN in the treatment naive subjects. CD4 cell counts remained stable for subjects who switched to receive GEN in the OL extension phase. The mean (SD) changes from baseline at selected time points were as follows: Week 192 GEN 366 (225.3) cells/µL; Week 108 D/C/F/TAF to GEN 73 (170.6) cells/µL; Week 108 All TDF to GEN 84 (160.0) cells/µL (Section 15.1, Table 10).

Resistance Testing Results:

Of the 273 subjects in the All GEN Analysis Set, 5 subjects (1.8%) were analyzed for the development of HIV-1 drug resistance (GEN 3 subjects; STB to GEN 1 subject; D/C/F/TAF to GEN 1 subject). One subject in the D/C/F/TAF to GEN group developed resistance to study drug (Subject PPD Subject PPD developed the reverse transcriptase (RT) mutations K70K/D/E/N and M184V, and the integrase mutation E92Q. This subject had a prior history of resistance with the development of the RT mutations K65K/R and M184M/I at the time of switch from D/C/F/TAF to GEN, and HIV-1 RNA remained suppressed < 50 copies/mL for > 1 year before experiencing virologic failure while receiving GEN.

Pharmacokinetic Results: No PK assessments were performed for this report. All PK data were presented in the interim Week 96 CSR.

Safety Results:

Overall, GEN was generally well tolerated by treatment naive subjects and those who switched to receive GEN. The median (Q1, Q3) exposure to double-blind and/or OL GEN were as follows: GEN 203.6 (194.9, 209.6) weeks; D/C/F/TAF to GEN 119.4 (113.9, 120.7) weeks; All TDF to GEN 132.1 (119.6, 143.9) weeks (Section 15.1, Table 6).

Adverse Events

Cumulatively, the percentages of subjects who had any AEs whilst receiving GEN were as follows: GEN 96.4% (108 of 112 subjects); D/C/F/TAF to GEN 85.7% (60 of 70 subjects); All TDF to GEN 93.4% (85 of 91 subjects) (Section 15.1, Table 12). The majority of AEs were Grade 1 or Grade 2 in severity. The percentages of subjects who had Grade 3 or 4 AEs were as follows: GEN 20.5% (23 of 112 subjects); D/C/F/TAF to GEN 8.6% (6 of 70 subjects); All TDF to GEN 9.9% (9 of 91 subjects). One subject in the GEN group had a Grade 3 or 4 AE (diarrhea) considered related to study drug by the investigator (Section 15.1, Table 18). Subjects who had any serious AEs (SAEs) were as follows: GEN 17.9% (20 of 112 subjects); D/C/F/TAF to GEN 7.1% (5 of 70 subjects); All TDF to GEN 11.0% (10 of 91 subjects). None of the SAEs reported were considered related to study drug by the investigator. One subject in the GEN group died as a result of trauma relating to alcohol consumption (Appendix 16.2, Listing 20). A total of 4.5%

(5 of 112 subjects) in the GEN group and no subjects in the switch groups had AEs that led to study drug discontinuation. Subject narratives for AEs that led to study drug withdrawal, SAEs, and death are provided in Section 15.2.

A total of 2 subjects (both in the GEN group) had 3 treatment-emergent Centers for Disease Control (CDC) Class C AIDS-defining events, as follows: nonserious proctitis herpes (Subject PPD and serious cytomegalovirus colitis extrapulmonary and mycobacterium avium complex infection (Subject PPD (Appendix 16.2, Listing 19).

The 3 most common AEs reported for subjects whilst receiving GEN were as follows:

- GEN: upper respiratory tract infection (30.4%; 34 subjects); nausea (25.9%; 29 subjects); diarrhea (23.2%; 26 subjects)
- D/C/F/TAF to GEN: upper respiratory tract infection (14.3%; 10 subjects); bronchitis (10.0%; 7 subjects); back pain, cough, and diarrhea (8.6%; 6 subjects each)
- All TDF to GEN: upper respiratory tract infection (18.7%; 17 subjects); back pain (14.3%; 13 subjects); cough and syphilis (13.2%; 12 subjects each) (Section 15.1, Table 13)

For the GEN group, the most common AEs considered related to study drug by the investigator were nausea (13.4%, 15 subjects), diarrhea, and fatigue (6.3%, 7 subjects each), and flatulence (5.4%, 6 subjects); for D/C/F/TAF to GEN, none of the AEs considered related to study drug by the investigator was reported for more than 1 subject, which were vomiting, abdominal pain, osteopenia, and irritability (1.4%, 1 subject each); for the All TDF to GEN group, AEs considered related to study drug by the investigator that were reported for greater than 1 subject were diarrhea and osteopenia (2.2%, 2 subjects each) (Section 15.1, Table 16).

Bone Safety

Whilst receiving GEN, 2 subjects in the GEN group and 4 subjects in the All TDF to GEN group had a treatment-emergent fracture event (GEN: pelvic fracture, rib fracture, facial bones fracture, and upper limb [arm] fracture; All TDF to GEN: femur fracture, ankle fracture, hand fracture, and hip fracture) (Section 15.1, Table 30). Treatment-emergent serious fracture events were reported as follows: GEN: pelvic fracture and upper limb (arm) fracture (1 subject), facial bone fracture and rib fracture (1 subject); All TDF to GEN: femur fracture and ankle fracture (1 subject each) (Appendix 16.2, Listing 36). None of the fracture events were considered related to study drug by the investigator and none resulted in discontinuation of study drug. Narratives for subjects who had fracture events are provided in Section 15.2.

For the GEN group, an initial decrease from baseline in the mean values for hip BMD seen at Week 48 and reported in the Week 96 CSR, stabilized through 192 weeks of treatment (Section 15.1, Figure 5.1). For the D/C/F/TAF to GEN group, an initial increase from baseline was observed at Week 24 following a switch to GEN, followed by a decrease at Week 48, which stabilized through 96 weeks of treatment. For the All TDF to GEN group, an increase from baseline was observed at Week 48 following a switch to GEN, which stabilized through 96 weeks of treatment.

For the GEN group, an initial decrease from baseline in the mean values for spine BMD seen at Week 48 and reported in the Week 96 CSR; the level of spine BMD decrease reduced from Week 96 through 144 weeks of treatment, before recovering to near baseline by Week 144

(Section 15.1, Figure 5.2). For the D/C/F/TAF to GEN group, progressive increases from baseline were observed at Week 24 through Week 96 following a switch to GEN. For the All TDF to GEN group, an increase from baseline was observed at Week 24 following a switch to GEN, which stabilized through 96 weeks of treatment.

The mean (SD) percentage change from baseline for the hip and spine for subjects in the GEN and switch groups at selected time points were as follows:

- Hip: Week 192 GEN −0.76% (4.188); Week 96 D/C/F/TAF to GEN −0.41% (3.979); Week 96 All TDF to GEN 1.16% (4.505) (Section 15.1, Table 28.1.1)
- Spine: Week 192 GEN 0.19% (3.859); Week 96 D/C/F/TAF to GEN 1.59% (4.403); Week 96 All TDF to GEN 1.84% (4.602) (Section 15.1, Table 28.1.2)

Few subjects in either the GEN or switch groups had shifts in hip or spine BMD clinical status while receiving GEN (Section 15.1, Tables 28.2.1 and 28.2.2).

Changes in BMD while receiving GEN were supported by the changes from baseline in the bone biomarker CTx for all treatment groups (Section 15.1, Table 29.1). As reported in the Week 96 CSR, increases from baseline were observed at Week 24 for the bone biomarker P1NP in the GEN group; these increases stabilized through 192 weeks of treatment. For the D/C/F/TAF to GEN group, changes from baseline were minimal following a switch to GEN through 96 weeks of treatment. For the All TDF to GEN group, decreases from baseline were observed at Week 48 following a switch to GEN, which subsequently stabilized through 96 weeks of treatment (Section 15.1, Table 29.2).

Renal Safety

There were no cases of proximal renal tubulopathy reported for any treatment groups whilst receiving GEN, and no subjects discontinued study drug due to a renal AE. Two subjects in the GEN group had events of renal failure; 1 SAE of acute renal failure due to volume depletion and 1 nonserious event of renal failure (reported as renal insufficiency; maximum serum creatinine 1.5 mg/dL) related to volume depletion and an SAE of pyelonephritis. Both events of renal failure resolved and were considered not related to study drugs by the investigator. Narratives for these subjects are provided in Section 15.2.

For the GEN group, increases from baseline in the mean values for serum creatinine seen at Week 2 and reported in the Week 96 CSR, stabilized through 192 weeks of treatment (Section 15.1, Figure 7). For the D/C/F/TAF to GEN group, a decrease from baseline was observed at Week 4 following a switch to GEN, which stabilized through 108 weeks of treatment. For the All TDF to GEN group, progressive decreases from baseline was observed at Week 2 through 108 weeks of treatment following a switch to GEN. Mean (SD) changes from baseline at selected time points were as follows: Week 192 GEN 0.02 (0.115) mg/dL; Week 108 D/C/F/TAF to GEN −0.06 (0.157) mg/dL; Week 108 All TDF to GEN −0.08 (0.115) mg/dL (Section 15.1, Table 31).

For the GEN group, decreases from baseline in the median values for $eGRF_{CG}$ seen at Week 2 and reported in the Week 96 CSR, stabilized through 192 weeks of treatment (Section 15.1, Figure 8.1). For the D/C/F/TAF to GEN group, progressive increases from baseline were observed at Week 4 through Week 60 following a switch to GEN, which subsequently stabilized through 108 weeks of treatment. For All TDF to GEN group, progressive increases from baseline

was observed at Week 2 through 108 weeks of treatment following a switch to GEN. The median (Q1, Q3) changes from baseline at selected time points were as follows: Week 192 GEN 0.2 (−11.1, 11.3) mL/min; Week 108 for D/C/F/TAF to GEN 4.7 (−3.2, 17.6) mL/min; Week 108 for All TDF to GEN 9.6 (1.6, 17.9) mL/min (Section 15.1, Table 32.1).

Observations for changes from baseline in $eGFR_{CKD-EPI}$ support those seen for $eGFR_{CG}$ (Section 15.1, Table 32.2).

For the GEN group, decreases from baseline in the median values for UPCR seen at Week 12 and reported in the Week 96 CSR, stabilized through 192 weeks of treatment (Section 15.1, Figure 10.1). For the D/C/F/TAF to GEN group, no consistent changes from baseline were observed through 96 weeks of treatment following a switch to GEN. For the All TDF to GEN group, a decrease was observed at Week 24 following a switch to GEN, which stabilized through 96 weeks of treatment. The median (Q1, Q3) percentage changes from baseline at selected time points were as follows: Week 192 GEN −7.2% (−35.7%, 45.2%); Week 96 D/C/F/TAF to GEN −3.8% (−32.4%, 36.9%); Week 96 All TDF to GEN −17.7% (−39.5%, 18.8 %) (Section 15.1, Table 34.1).

For the GEN group, decreases from baseline in the median values for UACR seen at Week 12, and reported in the Week 96 CSR, persisted through 192 weeks of treatment (Section 15.1, Figure 10.2). For the D/C/F/TAF to GEN group, no consistent changes from baseline were observed through 96 weeks of treatment following a switch to GEN. For the All TDF to GEN group, a decrease from baseline was observed at Week 24 following a switch to GEN, which stabilized through 96 weeks of treatment. The median (Q1, Q3) percentage changes from baseline at selected time points were as follows: Week 192 GEN 9.7% (−31.6%, 92.6%); Week 96 D/C/F/TAF to GEN −3.8% (−28.4%, 51.1%); Week 96 All TDF to GEN −10.0% (−36.1%, 65.0%) (Section 15.1, Table 34.2).

For the GEN group, no change from baseline in median value for urine RBP to creatinine ratio at Week 48 was seen and reported in the Week 96 CSR; however, a progressive increase was subsequently seen from Week 72 through 192 weeks of treatment (Section 15.1, Figure 9.1). For the D/C/F/TAF to GEN group, an increase from baseline was observed at Week 48 following a switch to GEN, which stabilized through 96 weeks of treatment. For the All TDF to GEN group, a decrease was observed at Week 24 following a switch to GEN, which stabilized through 96 weeks of treatment. The median (Q1, Q3) percentage changes from baseline at selected time points were as follows: Week 192 GEN 64.3% (14.3%, 122.9%); Week 96 D/C/F/TAF to GEN 6.8% (−18.3%, 46.9%); Week 96 All TDF to GEN −5.3% (−38.0%, 28.5%) (Section 15.1, Table 33.1).

For the GEN group, decreases from baseline in the median values for urine beta-2-microglobulin to creatinine ratio seen at Week 12 and reported in the Week 96 CSR, stabilized through 192 weeks of treatment (Section 15.1, Figure 9.2). For the D/C/F/TAF to GEN group, a decrease from baseline was observed at Week 24 following a switch to GEN, which stabilized through 120 weeks of treatment. For the All TDF to GEN group, a decrease was observed at Week 24 following a switch to GEN, which stabilized through 96 weeks of treatment. The median (Q1, Q3) percentage changes from baseline at selected time points were as follows: Week 192 GEN −35% (−51%, 4%); Week 96 D/C/F/TAF to GEN −13% (−48%, 19%); Week 96 All TDF to GEN −43% (−69%, 31%) (Section 15.1, Table 33.2).

There were no clinically relevant changes from baseline in median values for TmP/GFR, $FEPO_4$, and FEUA using serum creatinine adjusted or unadjusted values in any of the treatment groups whilst receiving GEN (Section 15.1, Tables 35.1.1 to 35.3.2).

Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for hematology and clinical chemistry in any treatment group whilst receiving GEN, and the median values were within the normal ranges. The majority of subjects in the GEN and switch groups had at least 1 laboratory abnormality reported (GEN 99.1%, 110 subjects; D/C/F/TAF to GEN 95.7%, 67 subjects; All TDF to GEN 100%, 91 subjects) (Section 15.1, Table 22). Most of the reported abnormalities were Grade 1 or 2. The percentages of subjects with Grade 3 or 4 laboratory abnormalities during the study were as follows: GEN 43.2% (48 subjects); D/C/F/TAF to GEN 27.1% (19 subjects); All TDF to GEN 29.7% (27 subjects). The most commonly reported Grade 3 or 4 laboratory abnormality in any treatment groups whilst receiving GEN were as follows: GEN: creatinine kinase (15.3%, 17 subjects); D/C/F/TAF to GEN: creatinine kinase and amylase (5.7%, 4 subjects each); All TDF to GEN: fasting LDL (9.9%, 9 subjects) (Section 15.1, Table 23).

Metabolic Laboratory Parameters

For the GEN group, increases from baseline in median values seen for total cholesterol, fasting direct LDL, fasting HDL, total cholesterol to HDL ratio, and triglycerides at Week 12 and reported in the Week 96 CSR, stabilized through 192 weeks of treatment (Section 15.1, Tables 26.1 to 26.6). For the D/C/F/TAF to GEN group, decreases from baseline were observed for total cholesterol, fasting direct LDL, total cholesterol to HDL ratio, and triglycerides at Week 24 following a switch to GEN, which stabilized through 96 weeks of treatment. For the All TDF to GEN group, increases from baseline were observed for total cholesterol, fasting direct LDL, fasting HDL, total cholesterol to HDL ratio, and triglycerides at Week 24 following a switch to GEN, which stabilized through 96 weeks of treatment.

Changes from baseline in median values for fasting glucose were minimal for treatment naive subjects and those who switched to receive GEN.

Median (Q1, Q3) changes from baseline in metabolic laboratory parameters at selected time points were as follows:

- Total cholesterol: Week 192 GEN 39 (17, 59) mg/dL; Week 96 D/C/F/TAF to GEN −14 (−30, 12) mg/dL; Week 96 All TDF to GEN 19 (−6, 40) mg/dL
- Fasting direct LDL: Week 192 GEN 24 (10, 40) mg/dL; Week 96 D/C/F/TAF to GEN −5 (−22, 16) mg/dL; Week 96 All TDF to GEN 11 (−7, 25) mg/dL
- Fasting HDL: Week 192 GEN 7 (−1, 15) mg/dL; Week 96 D/C/F/TAF to GEN 2 (−4, 8) mg/dL; Week 96 All TDF to GEN 4 (−2, 9) mg/dL
- Total cholesterol to HDL ratio: Week 192 GEN 0.3 (−0.3, 0.9); Week 96 D/C/F/TAF to GEN −0.4 (−0.9, 0.2); Week 96 All TDF to GEN 0.1 (−0.3, 0.5)
- Fasting triglycerides: Week 192 GEN 32 (2, 91) mg/dL; Week 96 D/C/F/TAF to GEN −22 (−69, 15) mg/dL; Week 96 All TDF to GEN 8 (−16, 43) mg/dL

- Fasting glucose: Week 192 GEN 5 (−3, 11) mg/dL; Week 96 D/C/F/TAF to GEN 1 (−9, 7) mg/dL; Week 120 All TDF to GEN 2 (−5, 12) mg/dL

The majority of graded hypercholesterolemia and fasting LDL abnormalities were Grade 1 or 2 (Section 15.1, Table 22). No Grade 4 hypercholesterolemia or fasting LDL abnormalities were reported. The percentages of subjects who had Grade 3 hypercholesterolemia or fasting LDL abnormalities were as follows:

- Hypercholesterolemia: GEN 4.5%, 5 of 110 subjects; D/C/F/TAF to GEN 1.4%, 1 of 69 subjects; All TDF to GEN 4.4%, 4 of 91 subjects
- Fasting LDL: GEN 13.6%, 15 of 110 subjects; D/C/F/TAF to GEN 4.3%, 3 of 69 subjects; All TDF to GEN 9.9%, 9 of 91 subjects

Whilst receiving GEN, graded fasting hypercholesterolemia was reported as follows: GEN 72.7% (80 subjects); D/C/F/TAF to GEN 39.1% (27 subjects); All TDF to GEN 58.2% (53 subjects).

CONCLUSIONS:

- Consistent with the data reported in the Week 96 CSR, high rates of virologic suppression were achieved and maintained, and mean CD4 cell count increased from baseline through 192 weeks of treatment with GEN in treatment naive subjects (Week 192 HIV-1 RNA [M = E]: 97.8%; mean change from baseline at Week 192 for CD4 cell count: 366 cells/μL).
- High rates of virologic suppression were maintained and CD4 cell counts remained stable for subjects who switched to receive GEN in the OL extension phase (Week 108 HIV-1 RNA [M = E]: D/C/F/TAF to GEN 98.5%; All TDF to GEN 97.5%; mean change from baseline at Week 108 for CD4 cell count: D/C/F/TAF to GEN 73 cells/μL; All TDF to GEN 84 cells/μL).
- Virologic resistance to study drug was noted in 1 subject in the D/C/F/TAF to GEN group during the OL extension phase.
- Genvoya was well tolerated by all treatment groups. None of the SAEs reported were considered related to study drug by the investigator.
- Incidence of fracture events was low and all fracture events were considered not related to study drug by the investigator for all treatment groups. For the GEN group, initial decrease from baseline in hip and spine BMD seen at Week 48 and reported in the Week 96 CSR, stabilized through 192 and 144 weeks of treatment, respectively, with spine BMD recovering to near baseline by Week 144. For subjects who switched to receive GEN in the OL extension phase, general increases from baseline at the hip and spine BMD were seen. The changes in BMD were supported by the change from baseline in the bone biomarkers (CTx and P1NP) all treatment groups.
- There were no cases of proximal renal tubulopathy and no discontinuation of study drug due to a renal AE for any treatment group. For the GEN group, increases from baseline in serum creatinine and decreases from baseline for eGFR seen as early as Week 2, stabilized through 192 weeks of treatment; these changes were consistent with data reported in the Week 96 CSR and the known nonpathologic inhibitory effect of COBI on tubular creatinine secretion.

For subjects who switched to receive GEN, generally decreases from baseline in serum creatinine and increases from baseline in $eGFR_{CG}$ were seen.

- The majority of the changes in the lipid parameters were seen in the first 24 weeks of GEN treatment in either the GEN or switch groups, and the values remained stable through 192 weeks of treatment for the GEN group and 96 weeks of treatment for the switch groups.