FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment
Name of Test Drug:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF, Genvoya® [GEN])
Dose and Formulation:	Fixed-dose combination tablet containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 10 mg of TAF
Indication:	HIV-1 Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-292-0112
Phase of Development:	Phase 3
IND No.:	111007
EudraCT No.:	2013-000516-25
ClinicalTrials.gov Identifier:	NCT01818596
Study Start Date:	27 March 2013 (First Subject Screened)
Study End Date:	31 July 2014 (Last Subject Last Observation for the Primary Endpoint) 18 July 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Gordon E Crofoot, MD, PA Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Christoph Carter, MD Telephone: PPD Fax: PPD
Report Date:	21 February 2019
Previous Report Date(s):	03 January 2017 (Interim Week 144 Clinical Study Report) 11 February 2016 (Interim Week 96 Clinical Study Report) 19 October 2015 (Interim Week 72 Clinical Study Report) 13 October 2014 (Interim Week 24 Clinical Study Report)

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-292-0112
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

Investigators: Multicenter study

Study Centers: Subjects were enrolled at a total of 71 study sites; 51 in the United States (US), 4 in Thailand, 4 in the United Kingdom (UK), 4 in Australia, 3 in Spain, 2 in France, and 1 each in the Dominican Republic, Mexico, and the Netherlands

Publications:

Pozniak A, Arribas JR, Gathe J, Gupta SK, Post FA, Bloch M, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48 week results from a single-arm, multi-center, open-label, Phase 3 study. J Acquir Immune Defic Syndr 2015.

Post FA, Tebas P, Clarke A, Cotte L, Short W, Abram ME, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected adults with renal impairment: 96-week results from a single-arm, multi-center, open-label Phase 3 study. J Acquir Immune Defic Syndr 2016.

Study Period:

27 March 2013 (First Subject Screened)
31 July 2014 (Last Subject Last Observation for the Primary Endpoint)
18 July 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives:

Study GS-US-292-0112 was conducted to evaluate safety, efficacy, and tolerability of elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (E/C/F/TAF; Genvoya® [GEN]) fixed-dose combination in human immunodeficiency virus (HIV)-infected adult patients with stable, mild to moderate renal impairment (subjects with baseline estimated glomerular filtration rate calculated using the Cockcroft-Gault (CG) equation [$eGFR_{CG}$] 30 to 69 mL/min, inclusive).

The primary objective of this study was as follows:

- To evaluate the effect of GEN on renal parameters at Week 24

The secondary objectives of this study were as follows:

- To evaluate the effect of GEN on renal parameters at Weeks 48, 96, and 144
- To measure the proportion of subjects achieving virologic response (HIV-1 RNA < 50 copies/mL, US Food and Drug Administration [FDA] defined snapshot algorithm) at Weeks 24, 48, 96, and 144
- To evaluate the safety and tolerability of GEN through 144 weeks of treatment

This final report describes results obtained until after the last subject completed or discontinued from the study.

Methodology:

This was an open-label, multicenter, multicohort study to assess the safety, tolerability, and efficacy of GEN in HIV-1 infected, adult subjects with mild to moderate renal impairment.

Subjects with a stable $eGFR_{CG}$ of 30 to 69 mL/min for 3 months prior to screening were enrolled into Cohort 1 if they were on antiretroviral (ARV) therapy (ART) and virologically suppressed, or were enrolled into Cohort 2 if they were ART-naive. Subjects enrolled in Cohort 1 switched treatment to GEN from their existing ARV regimen (referred to as "switch subjects" in this report); subjects in Cohort 2 initiated ART with GEN (referred to as "ART-naive subjects" in this report).

Number of Subjects (Planned and Analyzed):
Planned: Up to 200 subjects with screening $eGFR_{CG}$ of 30 to 69 mL/min, including at least 30 subjects with screening $eGFR_{CG}$ of 30 to 49 mL/min, who were either switch subjects or ART-naive subjects.

Analyzed (Section 15.1, Table 2):

- Enrolled: 252 subjects (Cohort 1: 246; Cohort 2: 6)
- Full Analysis Set (FAS): 248 (Cohort 1: 242; Cohort 2: 6)
- Safety Analysis Set: 248 (Cohort 1: 242; Cohort 2: 6)
- Hip dual-energy x-ray absorptiometry (DXA) Analysis Set: 242 (Cohort 1: 236; Cohort 2: 6)
- Spine DXA Analysis Set: 242 (Cohort 1: 236; Cohort 2: 6)

Diagnosis and Main Criteria for Inclusion:

- **Cohort 1 (Switch):** Eligible subjects were HIV-infected adults with plasma HIV-1 RNA concentrations at undetectable levels for at least 6 months and < 50 copies/mL at screening, cluster determinant 4 (CD4) cell count ≥ 50 cells/μL, no history of known resistance to EVG, FTC, or tenofovir disoproxil fumarate (TDF), and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening.
- **Cohort 2 (ART-Naive):** Eligible subjects were ART-naive, HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, CD4 cell count ≥ 50 cells/μL, a screening genotype showing sensitivity to EVG, FTC, and TDF, and stable $eGFR_{CG}$ 30 to 69 mL/min for 3 months prior to screening.

Duration of Treatment: Subjects were treated once daily with GEN for 144 weeks in this open-label study. At the Week 144 visit, subjects in countries where GEN was not available were given the option to continue in the study and receive study drug for another 48 weeks, or until the product became available through an access program, or until Gilead Sciences (Gilead) elected to discontinue the study in that country, whichever came first. For subjects in the UK only, after the Week 144 visit, subjects stopped taking study drug, completed a 30-day follow-up visit, and continued on standard of care.

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

Batch Numbers: CP1204B1, CP1208B1, CP1303B1, CP1307B1, CP1310B1, CP1311B1, CP1313B1, CP1314B1, CP1315B1, CP1402B1, CP1406B1, CP1505B1, CP1507B1, and CP1603B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: None

Criteria for Evaluation:

Efficacy:

The primary and secondary efficacy endpoints were presented in the Study GS-US-292-0112 Interim Weeks 24, 72, 96, and 144 Clinical Study Reports (CSRs).

Efficacy endpoints included in this final analysis are:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL
- The change from baseline in CD4 cell count and CD4%

Pharmacokinetics:

No pharmacokinetic (PK) or pharmacodynamic (PD) analyses were performed for this report; these analyses were presented in the Study GS-US-292-0112 Interim Week 24 CSR.

Safety:

The primary and secondary safety endpoints were presented in the Study GS-US-292-0112 Interim Weeks 24, 72, 96, and 144 CSRs.

The safety endpoints included in this final analysis are presented in this section.

Renal safety endpoints included change from baseline in $eGFR_{CG}$, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C (cysC) equation ($eGFR_{CKD\text{-}EPI,\ cysC}$) adjusted for age and sex, eGFR calculated using the CKD-EPI serum creatinine equation ($eGFR_{CKD\text{-}EPI,\ creatinine}$) adjusted for age, sex, and race, serum creatinine, serum cysC, proteinuria by urinalysis (dipstick), proteinuria by urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR), tubular proteinuria by urine retinol binding protein (RBP) to creatinine ratio and urine beta-2-microglobulin to creatinine ratio, changes in renal phosphate handling by serum phosphate, renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR), and urine fractional excretion of phosphate ($FEPO_4$), urine fractional excretion of uric acid (FEUA), and urine creatinine.

Additional safety assessments included the following: adverse events (AEs) identification, bone mineral density (BMD) using DXA, vital signs, weight, and clinical laboratory tests (chemistry,

hematology, urinalysis, and pregnancy testing) including parathyroid hormone (PTH).

Patient-Reported Outcomes:

Patient-reported outcomes using a health utilization assessment were collected by study site staff at baseline and each postbaseline visit.

Statistical Methods:

Efficacy:

The FAS was the primary efficacy analysis set and included all subjects who were enrolled into the study and received at least 1 dose of study drug.

The primary efficacy endpoint was the percentage of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 24 as defined by the US FDA-defined snapshot algorithm. The data for the primary efficacy endpoint were presented in the Study GS-US-292-0112 Interim Week 24 CSR.

The secondary efficacy endpoints were the proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 48, 96, and 144 as determined by the US FDA-defined snapshot algorithm and the proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 24, 48, 96, and 144 as determined by the US FDA-defined snapshot algorithm. The secondary efficacy endpoints were presented in the Study GS-US-292-0112 Interim Weeks 24, 72, 96, and 144 CSRs.

The percentage of subjects with HIV-1 RNA < 50 copies/mL as defined by the missing data imputation method: Missing = Excluded (M = E) was summarized by cohort and baseline $eGFR_{CG}$ for all visits using the FAS.

The change from baseline in CD4 cell count and CD4% were descriptively summarized by cohort and baseline $eGFR_{CG}$ at each postbaseline visit.

Virology Resistance:

Efficacy analyses at Weeks 24 (primary), 48 (secondary), 72, 96, and end of study (EOS) included the FAS who were enrolled into the study and received at least 1 dose of study drug. Details for resistance testing through EOS are provided in separate Virology Study Reports documenting the details of resistance testing in Study GS-US-292-0112 at each time point: Week 24 (PC-120-2020), Week 48/72 (PC-120-2027), Week 96 (PC-120-2028), and Week 144 (PC-292-2001).

Pharmacokinetics:

No PK or PD analyses were performed for this report; these were presented in the Study GS-US-292-0112 Interim Week 24 CSR.

Safety:

The Safety Analysis Set was the primary analysis set for all safety analyses and included all enrolled subjects who received at least 1 dose of study drug. All data collected up to 30 days after subjects permanently discontinued study drug were included in the safety summaries, unless specified otherwise.

The primary renal endpoints were defined as change from baseline at Week 24 in $eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ cysC}$, and $eGFR_{CKD\text{-}EPI,\ creatinine}$. The data for the primary renal endpoints were presented in the Study GS-US-292-0112 Interim Week 24 CSR and repeated with updated data

at Weeks 48, 72, 96, and 144 analyses.

Changes from baseline in $eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ cysC}$, and $eGFR_{CKD\text{-}EPI,\ creatinine}$ were summarized by cohort and baseline $eGFR_{CG}$ (< 50 mL/min versus ≥ 50 mL/min) and by cohort and pre-switch TDF use (with pre-switch TDF use versus without pre-switch TDF use), respectively, for each visit using descriptive statistics. Pre-switch TDF use was defined as subjects who took a TDF-containing regimen (such as Stribild®, Atripla®, Complera®, Truvada®, and Viread®) immediately prior to the first dose date of study drug.

Secondary renal endpoints included the following: actual GFR (aGFR) directly measured using iohexol clearance ($CL_{iohexol}$) for subjects enrolled in the PK/PD substudy (presented in the Study GS-US-292-0112 Interim Week 24 CSR); serum creatinine; serum cysC; serum phosphorus; proteinuria by urinalysis (dipstick); urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio; UPCR and UACR; and other biomarkers including TmP/GFR ratio, urine $FEPO_4$, urine FEUA, and urine creatinine. No aGFR analyses were performed for this report. The secondary renal endpoints were summarized by cohort and baseline $eGFR_{CG,}$ and by cohort and pre-switch TDF use, respectively, at each visit using descriptive statistics.

The AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0. Treatment-emergent AE data were summarized by cohort and baseline $eGFR_{CG}$.

Percentage changes from baseline in hip and spine BMD were summarized by cohort and pre-switch TDF use for each visit. For each subject and each visit, the clinical BMD status was defined for hip and spine BMD based on the corrected T-score. The number and percentage of subjects in each clinical BMD status (normal, osteopenia, and osteoporosis) were summarized by visit and by baseline clinical BMD status.

For each subject and each visit, the hip and spine BMD was classified into 6 categories based on percentage decrease or increase from baseline. The number and percentage of subjects in each category was summarized at each postbaseline visit by cohort and pre-switch TDF use.

Bone biomarkers included serum C-telopeptide, procollagen type 1 N-terminal propeptide (P1NP), and PTH. Changes in C-telopeptide, P1NP, and PTH were summarized by cohort and pre-switch TDF use at each visit (through Week 48 for C-telopeptide and P1NP) using descriptive statistics. No C-telopeptide or P1NP analyses were performed for this report.

The number and percentage of subjects who experienced fracture events was summarized by cohort and pre-switch TDF use.

Analyses of laboratory data were based on values reported in conventional units. No inferential statistics were generated. For the lipid panel and glucose, only measurements under fasting status were summarized.

Patient-Reported Outcomes:

A health utilization assessment was performed, whereby the number of hospitalizations, unplanned visits for a healthcare issue, and unplanned specialty care provider visits for a healthcare issue since the last study visit were summarized by cohort and baseline $eGFR_{CG}$ at each postbaseline visit and up to Week 240 (based on cumulative numbers).

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 252 subjects were enrolled in the study (246 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects); 248 subjects received at least 1 dose of study drug (242 Cohort 1 switch subjects and 6 Cohort 2 ART-naive subjects) (Section 15.1, Table 1).

Of the 248 treated subjects across both cohorts, 14.9% (37 subjects) of Cohort 1 switch subjects prematurely discontinued study treatment; all Cohort 2 ART-naïve subjects completed study treatment. The most common reasons for discontinuation of study drug in the Cohort 1 switch subjects were AE (12 of 242 subjects [5.0%]), lost to follow-up (7 of 242 subjects [2.9%]), and investigator's discretion (6 of 242 subjects [2.5%]). Across both cohorts, 85.1% (211 subjects) completed study treatment (Section 15.1, Table 1).

Cohort 1: Switch Subjects

The Cohort 1 switch study population is notable for older age, prevalent comorbidities, moderate renal impairment, and a high prevalence of clinically significant proteinuria at baseline, as described below (Section 15.1, Tables 3.1, 3.2, 4.1 and 4.2).

The majority of subjects were male (192 of 242 subjects [79.3%]), and the median age was 58 years (range: 24 to 82). The most common races were white (152 of 242 subjects [62.8%]), black (44 of 242 subjects [18.2%]), or Asian (34 of 242 subjects [14.0%]); most subjects were non-Hispanic/Latino (209 of 242 subjects [86.4%]) (Section 15.1, Tables 3.1 and 3.2).

Of 242 Cohort 1 switch subjects, 39.3% (95 subjects) had a medical history of hypertension and 13.6% (33 subjects) had a medical history of diabetes. The baseline median (Q1, Q3) values for CD4 count and CD4% were 632 cells/μL (456, 811) and 34.7% (26.4%, 41.1%), respectively. Overall, 236 of 242 subjects (97.5%) of subjects had HIV-1 RNA < 50 copies/mL at baseline. The most common HIV risk factor categories were homosexual sex (126 of 242 subjects [52.1%]) and heterosexual sex (99 of 242 subjects [40.9%]). The majority of subjects (180 of 242 subjects [74.4%]) had asymptomatic HIV-1 infection (Section 15.1, Table 4.1).

At baseline, the median (Q1, Q3) $eGFR_{CG}$ was 55.6 mL/min (45.7, 62.4). Overall, 80 of 242 subjects (33.1%) had $eGFR_{CG}$ < 50 mL/min. At baseline, 23 of 242 subjects (9.5%) had Grade 2 proteinuria by urinalysis (dipstick) and 56 of 242 subjects (23.1%) had Grade 1 proteinuria. The majority of subjects (154 of 242 subjects [63.6%]) were in CKD Stage 3 ($eGFR_{CG}$ 30 to 59 mL/min) (Section 15.1, Table 4.1).

At baseline, median levels of HIV-1 RNA and CD4 cell count were similar between subjects with baseline $eGFR_{CG}$ < 50 mL/min and $eGFR_{CG} \geq 50$ mL/min. Subjects with baseline $eGFR_{CG}$ < 50 mL/min had a higher incidence of symptomatic HIV infection (18 of 80 subjects [22.5%] versus 10 of 162 subjects [6.2%]) and acquired immunodeficiency syndrome (AIDS) (16 of 80 subjects [20.0%] versus 18 of 162 subjects [11.1%]) at baseline compared with subjects with baseline $eGFR_{CG} \geq 50$ mL/min. Median (Q1, Q3) $eGFR_{CG}$ at baseline was 42.6 mL/min (37.7, 45.7) and 60.3 mL/min (55.5, 65.0) for subjects with baseline $eGFR_{CG}$ < 50 mL/min and ≥ 50 mL/min, respectively (Section 15.1, Table 4.1).

Median baseline $eGFR_{CG}$ was similar between Cohort 1 subjects with pre-switch TDF use and those without pre-switch TDF use, with median (Q1, Q3) values of 58.3 mL/min (48.0, 63.5) and

53.0 mL/min (43.1, 59.5), respectively. The distribution of subjects who were in CKD Stage 2 or CKD Stage 3 differed between the 2 subgroups, with a lower percentage of Cohort 1 switch subjects with pre-switch TDF use in CKD Stage 3 (91 of 158 subjects [57.6%] versus 63 of 84 subjects [75.0%]) and a higher percentage of these subjects in CKD Stage 2 (63 of 158 subjects [39.9%] versus 20 of 84 subjects [23.8%]) as compared with Cohort 1 switch subjects without pre-switch TDF use. The incidence of proteinuria by urinalysis (any grade) was higher in Cohort 1 subjects with pre-switch TDF use than it was in those without pre-switch TDF use (Section 15.1, Table 4.2).

Cohort 2: ART-Naive Subjects

All 6 subjects were male, with a median age of 54 years (range: 46 to 65). The races were black (3 subjects), white (2 subjects), and Asian (1 subject), and most were non-Hispanic/Latino (5 subjects) (Section 15.1, Table 3.1).

The baseline median (Q1, Q3) values for HIV-1 RNA, CD4 count, and CD4% were 4.72 $\log_{10}$ copies/mL (4.01, 5.35), 397 cells/μL (184, 673), and 24.6% (11.7%, 28.8%), respectively. Four subjects had baseline HIV-1 RNA ≥ 50 to ≤ 100,000 copies/mL and 2 subjects had baseline HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL. The HIV risk factor categories were homosexual sex (3 subjects) and heterosexual sex (3 subjects). Five subjects had asymptomatic HIV-1 infection and 1 subject had symptomatic HIV-1 infection (Section 15.1, Table 4.1).

At baseline, the median (Q1, Q3) $eGFR_{CG}$ in Cohort 2 ART-naive subjects was 60.2 mL/min (45.0, 63.2). One of the 6 subjects had Grade 2 proteinuria. Three subjects were in CKD Stage 2 ($eGFR_{CG}$ 60 to 89 mL/min), and 3 subjects were in CKD Stage 3 ($eGFR_{CG}$ 30 to 59 mL/min) (Section 15.1, Table 4.1).

Efficacy Results:

Cohort 1: Switch Subjects

Efficacy analyses with respect to the primary efficacy endpoint and the secondary efficacy endpoints at Weeks 24, 48, 96, and 144, based on the US FDA-defined snapshot algorithm, were performed in the previous interim analyses and are not repeated in this final analysis. In this section, efficacy analyses based on the FAS from Weeks 144 to 192 (the visit with at least 5 subjects with nonmissing data) are provided.

High rates of virologic suppression were maintained when assessed using the M = E analysis following 144 weeks of treatment with GEN. Overall, 207 of 211 subjects (98.1%) of Cohort 1 switch subjects achieved HIV-1 RNA < 50 copies/mL at Week 144, based on the FAS. The rate of virologic suppression (HIV-1 RNA < 50 copies/mL) was similar for subjects with baseline $eGFR_{CG}$ < 50 mL/min (67 of 68 subjects [98.5%]) and baseline $eGFR_{CG}$ ≥ 50 mL/min (140 of 143 subjects [97.9%]) at Week 144 (Section 15.1, Table 11.1). Efficacy was maintained after Week 144, based on the M = E analysis, as the proportion of subjects with HIV-1 RNA < 50 copies/mL ranged from 97.2% to 100% from Weeks 156 to 192 (Section 15.1, Table 11.1).

CD4 cell counts remained stable during treatment with GEN through Week 144, with an overall mean (SD) change from baseline in CD4 cell count (observed data) based on the FAS of 14 cells/μL (176.3) at Week 144 (Section 15.1, Table 11.2). After Week 144, CD4 cell counts generally remained stable, as the mean (SD) change from baseline in CD4 cell count (observed data) ranged from -18 cells/μL (172.8) to 29 cells/μL (164.5) from Weeks 156 to 192 (Section 15.1, Table 11.2).

Cohort 2: ART-Naive Subjects

All 6 Cohort 2 ART-naive subjects had virologic suppression at Week 144 when assessed using the M = E analysis based on the FAS (Section 15.1, Table 11.1). The interpretation of results obtained after Week 144 was limited since only 1 or 2 subjects had available data through Week 192.

Following initiation of GEN, CD4 cell counts increased, with a mean (SD) change from baseline of 216 cells/μL (143.5) at Week 144 (Section 15.1, Table 11.2). The interpretation of results obtained after Week 144 was limited since only 1 or 2 subjects had available data through Week 192.

Virology Resistance Data:

A cumulative assessment of all resistance testing for the study is summarized below. Resistance analyses included the FAS of 248 subjects who were enrolled into the study and received at least 1 dose of study drug. Details for resistance testing through EOS are provided in separate Virology Study Reports documenting the details of resistance testing for Study GS-US-292-0112 at each time point: Week 24 (PC-120-2020), Week 48/72 (PC-120-2027), Week 96 (PC-120-2028), and Week 144 (PC-292-2001). Data listings are presented in Section 16.2, Virology Listings 1 to 4.

Cohort 1: Switch Subjects

Baseline Genotypic Analyses

For select subjects in Cohort 1, historical protease (PR)/reverse transcriptase (RT) genotypes were used, when available, since subjects entered the study with suppressed HIV-1 RNA (< 50 copies/mL) and plasma genotyping could not be performed.

Development of Resistance: Resistance Analysis Population

Of the 248 randomized and treated subjects in Study GS-US-292-0112 through the EOS, 4 subjects from Cohort 1 (4 of 242 subjects [1.7%]; Subjects PPD PPD PPD and PPD met the virologic failure criteria and were included in the Resistance Analysis Population (RAP).

Four subjects in Cohort 1 were evaluated for the development of resistance through the EOS. Three of the four subjects had resistance mutations detected while on GEN due either to reinfection (n = 1), documented preexistence (n = 1), or emergent resistance (n = 1).

At Week 24 the first subject with documented resistance (Subject PPD had multiple nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)-R mutations (M184V, M41L, L210W, T215Y, T69SVS insertion, and F116Y) detected with phenotypic resistance to both tenofovir (TFV) (fold change [FC] = 10.0) and FTC (FC > 87). The primary integrase (IN) strand transfer inhibitor (INSTI)-R T66I in IN was also detected along with phenotypic resistance to EVG (FC = 11.9). Deep-sequencing analysis of pooled plasma samples from the baseline visit (23 July 2013) revealed no evidence of pre-existing genotypic resistance mutations. In addition, the HIV-1 subtype at this baseline visit was determined to be subtype C which differed from the subtype B detected at both Week 24 Retest visits. Multiple documented high-risk sexual encounters (e.g. unprotected sex with an intravenous drug using sex worker) while on study and emergence of subtype B HIV suggest that the sudden appearance of

resistance at Week 24 was likely due to reinfection with a distinct HIV isolate. Subject PPD was included in the RAP but later resuppressed HIV-1 RNA to < 50 copies/mL while continuing study drug and was not included in the Final RAP. The second subject with documented preexisting resistance (Subject PPD demonstrated confirmed virologic rebound followed by persistent low-level viremia and was included in the Final RAP. The third subject with emergent resistance (Subject PPD demonstrated virologic rebound and was included in the Final RAP but later achieved HIV-1 RNA reduction to 70 copies/mL while continuing study drugs. The fourth subject (PPD was negative for resistance mutations against study drugs and was included in the Final RAP.

Development of Resistance: Final Resistance Analysis Population

The Final RAP comprised 3 subjects (1.2%) in Cohort 1.

Subjects PPD PPD and PPD from Cohort 1 (switch subjects) had confirmed rebound (HIV-1 RNA ≥ 50 copies/mL) and were included in the Final RAP.

Subject PPD carried pre-existing RT resistance mutations D67N, K70R, and K219Q, and the PR resistance mutation L90M at the time of viral rebound. These mutations were present prior to the start of treatment with GEN, and reflected prior treatment history. Reduced susceptibility to TFV was noted at Week 48 (TFV FC = 2.02), but phenotypic sensitivity to FTC and EVG was maintained. The subject has shown steady low-level viremia while receiving GEN treatment.

Subject PPD had multiple NRTI-associated resistance mutations (M184V, K65R, and A62A/V), non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated resistance mutations (K101E and E138A), and INSTI-associated resistance mutations (E138K, S147G, and Q148R) with phenotypic resistance to TFV (FC = 1.43), FTC (FC > 82), and EVG (FC > 124) detected at the time of virologic failure, but lacked an available historical genotype. Study drug was discontinued due to lack of efficacy; however, at the early study drug discontinuation (ESDD) visit (21 April 2014), HIV-1 RNA was 70 copies/mL prior to switching to a new regimen of darunavir + ritonavir + etravirine + maraviroc.

Subject PPD was tested and found to have no genotypic or phenotypic resistance to any study drug.

Cohort 2: ART-Naive Subjects

Baseline Genotypic Analyses

All subjects enrolled in Study GS-US-292-0112 Cohort 2 had genotyping of the PR/RT genes and the IN gene performed at screening.

Development of Resistance

Of the 248 randomized and treated subjects in Study GS-US-292-0112 through the EOS, no subjects from Cohort 2 (0 of 6 subjects [0%]) met the virologic failure criteria and no subjects were included in the RAP. The Final RAP therefore comprised 0 subjects.

Pharmacokinetics/Pharmacodynamics Results: Pharmacokinetic and PD results were presented in the Study GS-US-292-0112 Interim Week 24 CSR. No PK or PD analyses were performed for this final report.

Safety Results:

Cohort 1: Switch Subjects

Genvoya was well tolerated in this study in Cohort 1 switch subjects through a median duration of study drug exposure of 144.4 weeks (Section 15.1, Table 6).

Renal Safety

Safety analyses with respect to the primary and secondary endpoints at Weeks 24, 48, 96, and 144, were performed in the previous interim analyses. In this section, safety endpoints defined for this final analysis were assessed using finalized data.

Overall, 4 subjects had renal serious adverse events (SAEs); none of the events resulted in discontinuation of study drug or were considered related to study drug by the investigator and most resolved: acute kidney injury (2 subjects), CKD, and urinary retention (Section 15.1, Tables 12.8, 12.9; and Section 16.2, Listings 21.1 and 22). In these 4 subjects, the renal SAEs occurred prior to the Week 144 data cut and have been discussed in the previous CSRs. No new renal SAEs were reported in this final analysis. Five subjects had renal AEs that resulted in discontinuation of study drug through Week 96 (Section 15.1, Table 12.10); there were no subjects with renal AEs leading to discontinuation of study drug after Week 96. Three of the events were considered unrelated to study drug by the investigator (nephropathy in 2 subjects, and CKD) and 2 were considered related to study drug by the investigator (nephropathy and renal failure) (Section 16.2, Listing 22). There were no subjects with treatment-emergent proximal renal tubulopathy (or Fanconi Syndrome) (Section 15.1, Table 12.2).

There were no clinically significant changes from baseline in serum creatinine for Cohort 1 switch subjects through Week 192 (Section 15.1, Table 10.1.4), with no clinically significant differences in serum creatinine results based on baseline $eGFR_{CG}$ or pre-switch TDF use (Section 15.1, Table 10.2.4). Graded laboratory abnormalities for serum creatinine were reported for 108 of 242 subjects (44.6%) (baseline $eGFR_{CG} < 50$ mL/min group 34 of 80 subjects [42.5%]; baseline $eGFR_{CG} \geq 50$ mL/min group 74 of 162 subjects [45.7%]) (Section 15.1, Table 13). Most of these abnormalities were Grade 1 or 2 (Section 15.1, Table 13). Grade 3 serum creatinine abnormalities were reported for 9 of 242 subjects (3.7%); baseline $eGFR_{CG} < 50$ mL/min group 6 of 80 subjects [7.5%]; baseline $eGFR_{CG} \geq 50$ mL/min group 3 of 162 subjects [1.9%]) (Section 15.1, Table 13). Grade 4 serum creatinine abnormalities were reported for 1 of 242 subjects (0.4%) overall (baseline $eGFR_{CG} < 50$ mL/min group 1 of 80 subjects [1.3%]) (Section 15.1, Table 13).

Overall, improvements (increases) from baseline in eGFR were observed for Cohort 1 switch subjects at Week 192, irrespective of filtration marker or equation (Section 15.1, Tables 10.1.1 to 10.1.3). Subjects with moderate renal impairment ($eGFR_{CG} < 50$ mL/min) showed greater improvements in eGFR compared with subjects with mild renal impairment ($eGFR_{CG} \geq 50$ mL/min) at Week 192 (irrespective of filtration marker or equation) (Section 15.1, Tables 10.1.1 to 10.1.3). In addition, subjects with pre-switch TDF use showed greater improvements in eGFR at Week 180 compared with subjects without pre-switch TDF use (irrespective of filtration marker or equation; results are discussed up to Week 180 due to small number of subjects with nonmissing data beyond Week 180) (Section 15.1, Tables 10.2.1 to 10.2.3).

Overall, there were no clinically significant changes from baseline in serum cysC or serum

phosphorus for Cohort 1 switch subjects through Week 192 (Section 15.1, Tables 10.1.5 and 10.1.6, respectively).

Proteinuria toxicity grade change from baseline grade was only summarized up to Week 144 due to a decline in subject numbers beyond Week 144. Most subjects had either no change from baseline or an improvement from baseline (toxicity grade decreased at least 1 grade from baseline) in proteinuria toxicity grade at Week 144. Overall, 56 of 67 subjects (83.6%) had proteinuria grade improvements and 11 of 203 subjects (5.4%) had proteinuria grade worsening (Section 15.1, Table 10.1.7). Improvements from baseline were more common in those subjects with pre-switch TDF use than they were in those without pre-switch TDF use. At Week 144, 45 of 51 subjects (88.2%) with pre-switch TDF use versus 11 of 16 subjects (68.8%) without pre-switch TDF use had proteinuria grade improvements, and 4 of 137 subjects (2.9%) with pre-switch TDF use versus 7 of 66 subjects (10.6%) without pre-switch TDF use had proteinuria grade worsening (Section 15.1, Table 10.2.7).

In Cohort 1 switch subjects overall, significant improvements (declines) in proteinuria, albuminuria, and tubular proteinuria (urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio) were observed at Week 2 and persisted through Week 144 and beyond (to Week 192); the median percent changes from baseline at Week 144 were as follows: UPCR –45.7% (–70.8% at Week 192) (Section 15.1, Table 10.1.10.1); UACR –35.5% (–44.9% at Week 192) (Section 15.1, Table 10.1.11.1); urine RBP to creatinine ratio –63.8% (–85.6% at Week 192) (Section 15.1, Table 10.1.8); and beta-2-microglobulin to creatinine ratio –81.9% (–75.5% at Week 192) (Section 15.1, Table 10.1.9). These changes from baseline at Week 144 represent a 53% improvement in median UPCR (Section 15.1, Table 10.1.10.1), a 58% improvement in median UACR (Section 15.1, Table 10.1.11.1), a 75% improvement in median RBP to creatinine ratio (Section 15.1, Table 10.1.8), and an 85% improvement in median beta-2-microglobulin to creatinine ratio (Section 15.1, Table 10.1.9). Improvements in renal parameters were particularly marked in the subjects with pre-switch TDF use, while renal function in subjects without pre-switch TDF use did not have significant changes (Section 15.1, Tables 10.2.10.1, 10.2.11.1, 10.2.8, and 10.2.9). There were no clinically significant changes from baseline through Week 192 in TmP/GFR, urine $FEPO_4$, urine FEUA, or urine creatinine for Cohort 1 switch subjects overall (Section 15.1, Tables 10.1.12 to 10.1.15), regardless of pre-switch TDF use (Section 15.1, Tables 10.2.12 to 10.2.15).

Adverse Events

Overall, at least 1 AE was reported in 231 of 242 subjects (95.5%) of Cohort 1 switch subjects (baseline $eGFR_{CG} < 50$ mL/min 76 of 80 subjects [95.0%]; baseline $eGFR_{CG} \geq 50$ mL/min 155 of 162 subjects [95.7%]) (Section 15.1, Table 12.1). Two treatment-emergent deaths (both Cohort 1) (Section 15.1, Table 12.1 and Section 16.2, Listing 26) and 1 non-treatment emergent death (Cohort 1) (Section 16.2, Listing 26) were reported: 1 subject (baseline $eGFR_{CG} \geq 50$ mL/min) died of cardiopulmonary arrest, 1 subject (baseline $eGFR_{CG} < 50$ mL/min) died of cardiac arrest (Section 16.2, Listing 26), and 1 subject (baseline $eGFR_{CG} \geq 50$ mL/min) died of myocardial infarction more than 30 days after the last dose of study drug (non-treatment emergent) (Section 16.2, Listing 21.1). The events leading to the deaths were considered unrelated to study drug by the investigator (Section 16.2, Listing 21.1). All 3 deaths have been discussed in the previous CSRs. No new deaths were reported in this final analysis. Grade 3 or 4 AEs were reported in 54 of 242 subjects (22.3%) of Cohort 1 switch subjects (baseline $eGFR_{CG}$

< 50 mL/min 23 of 80 subjects [28.8%]; baseline $eGFR_{CG} \geq 50$ mL/min 31 of 162 subjects [19.1%]) (Section 15.1, Table 12.4).

At least 1 SAE was reported in 55 of 242 subjects (22.7%) of Cohort 1 switch subjects (baseline $eGFR_{CG} < 50$ mL/min 20 of 80 subjects [25.0%]; baseline $eGFR_{CG} \geq 50$ mL/min 35 of 162 subjects [21.6%]) (Section 15.1, Table 12.8); all SAEs were considered unrelated to study drug by the investigator (Section 15.1, Table 12.9).

Adverse events considered related to study drug by the investigator were reported in 73 of 242 subjects (30.2%) of Cohort 1 switch subjects (baseline $eGFR_{CG} < 50$ mL/min 27 of 80 subjects [33.8%]; baseline $eGFR_{CG} \geq 50$ mL/min 46 of 162 subjects [28.4%]) (Section 15.1, Table 12.5). The most commonly reported AEs considered related to study drug by the investigator in Cohort 1 switch subjects were diarrhea and dizziness (8 of 242 subjects [3.3% for each AE]); and headache, hypercholesterolemia, nausea, constipation, and osteopenia (5 of 242 subjects [2.1% for each AE]) (Section 15.1, Table 12.5). The majority of study drug-related AEs were Grade 1 or 2 in severity (Section 15.1, Table 12.7); 4 Cohort 1 switch subjects each had nonserious Grade 3 AEs considered related to study drug: blood creatine phosphokinase increased (baseline $eGFR_{CG} < 50$ mL/min group), gastroesophageal reflux disease (baseline $eGFR_{CG} \geq 50$ mL/min), hypercholesterolemia and low density lipoprotein (LDL) increased (baseline $eGFR_{CG} \geq 50$ mL/min), and diabetes mellitus inadequate control (baseline $eGFR_{CG} < 50$ mL/min). One Cohort 1 switch subject (baseline $eGFR_{CG} < 50$ mL/min) had a nonserious Grade 3 AE of chronic kidney disease that was considered related to study drug in the Interim Week 144 CSR; however, in the final analysis, the AE was updated as unrelated to study drug by the investigator (Section 15.1, Table 12.7 and Section 16.2, Listing 20).

Adverse events leading to premature study drug discontinuation were reported for 12 of 242 (5.0%) of Cohort 1 switch subjects (baseline $eGFR_{CG} < 50$ mL/min 8 of 80 subjects [10.0%]; baseline $eGFR_{CG} \geq 50$ mL/min 4 of 162 subjects [2.5%]) (Section 15.1, Table 12.10); of these, 4 subjects (2 with baseline $eGFR_{CG} < 50$ mL/min and 2 with baseline $eGFR_{CG} \geq 50$ mL/min) had an AE leading to premature study drug discontinuation considered related to study drug by the investigator (sleep disorder, renal failure, nephropathy, and choking, respectively) (Section 16.2, Listing 22). There were no new discontinuations of study drug due to AEs reported after the Week 96 data cutoff date.

No pregnancies were reported during the study (Section 16.2, Listing 36).

The most commonly reported AEs were bronchitis and upper respiratory tract infection (39 of 242 subjects each [16.1%]), arthralgia (35 of 242 subjects [14.5%]), and diarrhea (32 of 242 subjects [13.2%]) (Section 15.1, Table 12.2). No new AE of osteopenia or osteoporosis was reported in this final analysis (Section 16.2, Listing 19). The FTC associated AEs continue to be low (Section 15.1, Table 12.2).

No new potential cardiovascular or cerebrovascular events were reported in this final analysis (Section 15.1, Table 18.3).

Bone Safety

Fracture events were reported in 6 of 242 subjects (2.5%) of Cohort 1 switch subjects (with pre-switch TDF use 4 of 158 subjects [2.5%]; without pre-switch TDF use 2 of 84 subjects [2.4%]). (Section 15.1, Table 20.9). Of these fracture events, 1 event was an additional fracture reported in this final analysis (rib fracture; subject with pre-switch TDF use [Section 16.2,

Listing 24]).None of the fracture AEs were considered related to the study drug by the investigator or resulted in discontinuation of study drug (Section 15.1, Table 12.10). One fracture AE (lumbar vertebral fracture) was initially reported as related to study drug by the investigator. However, additional information provided by the investigator through a separate safety report indicated that the fracture was due to trauma (possibly related to the use of lisinopril-induced hypotension), and this AE was ultimately determined to be not related to study drug (Section 15.2). All fracture events were the result of trauma, and none were reported as fragility fractures. Narratives for subjects who had fracture events are provided in Section 15.2.

Overall, hip and spine BMD increased for Cohort 1 switch subjects after switching to GEN (Section 15.1, Tables 20.1 and 20.2). Mean (SD) percentage increases from baseline were observed in hip BMD (Week 144: 2.365% [4.8586%]; Week 192: 1.747% [3.3018%]) (Section 15.1, Table 20.1) and spine BMD (Week 144: 2.771% [4.9770%]; Week 192: 4.402% [3.1917%]) (Section 15.1, Table 20.2). At Week 144, median (Q1, Q3) percentage changes from baseline in hip BMD were higher in subjects with pre-switch TDF use (2.283% [0.357%, 4.757%]) than they were in those without pre-switch TDF use (0.994% [−1.498%, 3.271%]) (Section 15.1, Table 20.1). At Week 144, median (Q1, Q3) percentage changes from baseline in spine BMD were higher in subjects with pre-switch TDF use (3.747% [0.694%, 6.001%]) than they were in those without pre-switch TDF use (0.604% [−1.581%, 4.134%]) (Section 15.1, Table 20.2). The percentage changes from baseline in hip and spine BMD were statistically significant at Week 144 for Cohort 1 switch subjects with pre-switch TDF use and for Cohort 1 overall ($p < 0.001$) (Section 15.1, Tables 20.1 and 20.2); the percentage change from baseline in spine BMD was also statistically significant at Week 144 for subjects without pre-switch TDF use ($p = 0.030$) (Section 15.1, Table 20.2). The trend observed between subjects with pre-switch TDF use versus without pre-switch TDF use continued beyond Week 144 though Week 192; however, given the decline in subject numbers, the interpretation of the data is limited.

There was evidence for an improvement in hip and spine BMD after switching to GEN, when assessed using a threshold of 3% for changes from baseline at Week 144; higher percentages of subjects had increases versus decreases from baseline in BMD at both hip (38.4% versus 8.9%) (Section 15.1, Table 20.3) and spine (47.4% versus 10.3%) (Section 15.1, Table 20.4). Also, higher percentages of subjects had improvement versus worsening from baseline in BMD clinical status (assessed using BMD T-scores) at both hip (14 of 101 subjects [13.9%] versus 3 of 179 subjects [1.7%]) (Section 15.1, Table 20.6) and spine (14 of 91 subjects [15.4%] versus 3 of 179 subjects [1.7%]) (Section 15.1, Table 20.7) at Week 144. Among the Cohort 1 switch subjects with osteoporosis at baseline, improved osteopenia was observed in 6 of 11 subjects (54.5%) overall for hip BMD (Section 15.1, Table 20.6) and in 6 of 15 subjects (40.0%) overall for spine BMD (Section 15.1, Table 20.7). Among the Cohort 1 switch subjects with osteopenia at baseline, worsening of osteoporosis was observed in 1 of 90 subjects (1.1%) overall for hip BMD (Section 15.1, Table 20.6) and in 1 of 76 subjects (1.3%) overall for spine BMD (Section 15.1, Table 20.7). Results beyond Week 144 for the above mentioned endpoints were not summarized due to the reduced sample size.

Overall, there were no clinically significant changes from baseline in PTH through Week 192 (Section 15.1, Table 20.8). Increases from baseline in PTH were observed for Cohort 1 switch subjects without pre-switch TDF use, while no clinically significant changes from baseline were observed in those with pre-switch TDF use (Section 15.1, Table 20.8).

Laboratory Abnormalities

There were no clinically significant changes from baseline in median values for hematology or clinical chemistry parameters, and all median values were generally within normal ranges (Section 15.1, Tables 16.1 to 16.13 and 17.1 to 17.21).

Each of the 242 Cohort 1 switch subjects had at least 1 laboratory abnormality reported through the EOS (Section 15.1, Table 13). The majority of laboratory abnormalities were Grade 2 or 3 in severity (Section 15.1, Table 13). The most commonly observed Grade 3 or 4 laboratory abnormalities in Cohort 1 switch subjects were LDL (fasting) (37 subjects), total cholesterol (fasting, hypercholesterolemia) (21 subjects), serum glucose (fasting, hyperglycemia) (14 subjects), serum glucose (nonfasting, hyperglycemia) (13 subjects), and creatine kinase (13 subjects) (Section 15.1, Table 14). Importantly, rates of laboratory abnormalities associated with FTC use were low and generally balanced between the baseline $eGFR_{CG}$ groups despite higher FTC exposures in the $eGFR_{CG} < 50$ mL/min group compared with historical data from HIV-infected subjects with normal renal function (Study GS-US-292-0112 Interim Week 24 CSR).

Metabolic Laboratory Parameters

For Cohort 1 switch subjects, statistically significant median increases from baseline to Week 144 were observed in fasting triglycerides and fasting glucose (Section 15.1, Table 18.1.5 and Table 18.2) and the trend continued beyond Week 144, but not in fasting total cholesterol (Section 15.1, Table 18.1.1), fasting direct LDL cholesterol (Section 15.1, Table 18.1.2), or fasting total cholesterol to high density lipoprotein (HDL) ratio (Section 15.1, Table 18.1.4). Generally, median changes from baseline through Week 192 increased in subjects with pre-switch TDF use and decreased in subjects without pre-switch TDF use.

Cohort 2: ART-Naive Subjects

Genvoya was well tolerated in this study in Cohort 2 ART-naive subjects through a median duration of study drug exposure of 144.1 weeks (Section 15.1, Table 6). Only 6 Cohort 2 ART-naive subjects were enrolled, with 1 to 2 subjects with data beyond Week 144; therefore, limited summaries (up to Week 144 for the by visit summary) are provided for these subjects and interpretation of their data should be made with caution.

Renal Safety

Safety analyses with respect to the primary and secondary endpoints at Weeks 24, 48, 96, and 144, were performed in the previous interim analyses. In this section, safety endpoints defined for this final analysis were assessed using finalized data.

No Cohort 2 ART-naive subject had a renal SAE or a renal AE that resulted in discontinuation of study drug (Section 15.1, Table 12.10).

Overall, there were no clinically significant changes from baseline in serum creatinine (Section 15.1, Table 10.1.4), eGFR (regardless of filtration marker or equation) (Section 15.1, Tables 10.1.1 to 10.1.3), serum cysC (Section 15.1, Table 10.1.5), serum phosphorus (Section 15.1, Table 10.1.6), UPCR (Section 15.1, Table 10.1.10.1), UACR (Section 15.1, Table 10.1.11.1), urine RBP to creatinine ratio (Section 15.1, Table 10.1.8), urine FEUA (Section 15.1, Table 10.1.14), TmP/GFR (Section 15.1, Table 10.1.12), urine $FEPO_4$ (Section 15.1, Table 10.1.13), or urine creatinine (Section 15.1, Table 10.1.15) through Week 144 for Cohort 2 ART-naive subjects. Graded laboratory abnormalities for serum

creatinine (Grade 1 and Grade 3) were reported for 2 Cohort 2 ART-naive subject (Section 15.1, Table 13). There were no changes from baseline in proteinuria toxicity grade at Week 144 (Section 15.1, Table 10.1.7).

Overall, median urine beta-2-microglobulin to creatinine ratio decreased from baseline for Cohort 2 ART-naive subjects. Median percentage changes from baseline were as follows: Week 2: 43.4%; Week 96: –45.9%; Week 144: −3.6% (Section 15.1, Table 10.1.9).

Adverse Events

For Cohort 2 ART-naive subjects, at least 1 AE was reported for each of the 6 subjects (Section 15.1, Table 12.1). An SAE was reported in 1 subject (Grade 4 suicidal ideation); this was the only Grade 3 or 4 AE reported and the event was considered unrelated to study drug by the investigator (Section 16.2, Listing 20). The AEs considered related to study drug by the investigator were reported in 2 subjects (dyslipidemia [Grade 2] and hyperlipidemia [Grade 1], respectively) (Section 15.1, Table 12.5 and Section 16.2, Listing 19). No AEs leading to premature study drug discontinuation or deaths were reported for this cohort (Section 15.1, Table 12.10).

No Cohort 2 ART-naive subject had a potential cardiovascular or cerebrovascular event during the study (Section 15.1, Table 18.3).

Bone Safety

No fracture events occurred in Cohort 2 ART-naive subjects (Section 15.1, Table 20.9). Mean (SD) percentage decreases from baseline were observed in hip BMD (Week 144: −0.944% [2.3880%]) and spine BMD (Week 144: −0.033% [5.0742%]) for Cohort 2 ART-naive subjects (Section 15.1, Tables 20.1 and 20.2). At Week 144, a decrease from baseline > 3% in hip BMD was observed in 1 Cohort 2 ART-naive subject; no increases from baseline > 3% in hip BMD were observed for Cohort 2. Decreases from baseline > 3% in spine BMD were observed in 2 Cohort 2 ART-naive subjects at Week 144 (1 decrease > 3% to ≤ 5%; 1 decrease > 5%); an increase in spine BMD of > 5% was observed in 1 Cohort 2 ART-naive subject (Section 15.1, Tables 20.4 and 20.5). Overall, there were no clinically significant changes from baseline in PTH through Week 144 for Cohort 2 ART-naive subjects (Section 15.1, Table 20.8).

Laboratory Abnormalities

There were no clinically significant changes from baseline in median values for hematology or clinical chemistry parameters through Week 144 (Section 15.1, Tables 16.1 to 16.13 and 17.1 to 17.21). Four subjects had Grade 3 or 4 laboratory abnormalities throughout the study; 2 subjects had Grade 3 increased LDL, 1 subject had Grade 3 increased amylase and Grade 4 increased creatine kinase, and 1 subject had Grade 3 increased LDL and Grade 3 increased creatinine (Section 16.2, Listing 34).

Patient-Reported Outcomes:

Cohort 1: Switch Subjects

Through Week 144, the percentages of Cohort 1 switch subjects overall who were hospitalized, had unplanned visits for a healthcare issue, or had unplanned specialty care provider visits for a healthcare issue were 4 of 205 subjects (2.0%), 17 of 205 subjects (8.3%), and 15 of 205 subjects (7.3%), respectively. Through Week 192, the percentages of Cohort 1 switch subjects overall

who were hospitalized, had unplanned visits for a healthcare issue, or had unplanned specialty care provider visits for a healthcare issue were 0 of 17 subjects (0%), 1 of 17 subjects (5.9%), and 1 of 17 subjects (5.9%), respectively. No clinically meaningful trends or changes at any assessment time point were observed (Section 15.1, Table 23.1).

Cohort 2: ART-Naive Subjects

In Cohort 2 ART-naive subjects through Week 144, no subjects were hospitalized, had unplanned visits for a healthcare issue, or had unplanned specialty care provider visits for a healthcare issue. No clinically meaningful trends or changes at any assessment time point were observed (Section 15.1, Table 23.1).

CONCLUSIONS:

Follow-up of subjects through the EOS confirms the conclusions from the Week 144 analysis and are as follows:

- Genvoya was well tolerated in subjects with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min). There were no new renal SAEs and no new discontinuations of study drug due to renal AEs since the Week 144 data cut, and no AEs of proximal renal tubulopathy (or Fanconi Syndrome) were reported.
- Overall, subjects with mild to moderate renal impairment who switched to GEN (containing TAF) had statistically significant improvements in eGFR at Week 144 and the trend continued beyond Week 144. Furthermore, these subjects had rapid, persistent, and clinically significant improvements in proteinuria, albuminuria, proximal renal tubular function, and BMD.
- The subset of subjects with $eGFR_{CG} < 50$ mL/min, who currently require dose adjustment for both TDF and FTC, had improvements in eGFR and significant improvements in tubular function through 192 weeks after switching to once daily GEN without dose-limiting AEs.
- The subset of subjects with pre-switch TDF use showed statistically significant improvements in eGFR at Week 144 and the trend continued beyond Week 144, while those subjects without pre-switch TDF use showed no significant changes.
- No notable changes from baseline in median values for hematology or clinical chemistry were observed in either cohort through Week 192, and the majority of reported laboratory abnormalities were Grade 2 or 3.
- Median changes from baseline in metabolic laboratory parameters through Week 192 demonstrated a trend toward increase in all parameters for subjects with pre-switch TDF use and a trend toward decrease in most parameters for subjects without pre-switch TDF use.
- In Cohort 1 subjects who switched treatment to GEN, 207 of 211 subjects (98.1%) maintained virologic suppression (HIV-1 RNA < 50 copies/mL) and had stable CD4 cell counts through Week 144 and beyond. Efficacy was maintained after Week 144, as the proportion of subjects with HIV-1 RNA < 50 copies/mL ranged from 97.2% to 100% from Weeks 156 to 192 and CD4 cell counts generally remained stable.
- In Cohort 1, 4 of 242 subjects (1.7%) were analyzed and 3 subjects showed resistance to multiple drug classes.

- One subject with HIV-1 subtype C virus at baseline had detectable resistance to all study drugs as well as nonstudy drugs at virologic failure with an HIV-1 subtype B variant, possibly due to reinfection. This subject achieved HIV-1 RNA resuppression to < 20 copies/mL with continued E/C/F/TAF treatment prior to switching to a new regimen.
- The second subject showed persistent low-level viremia and drug resistance mutations to NRTI and protease inhibitors that were documented in a historical genotype prior to initiating E/C/F/TAF treatment.
- The third subject had NRTI resistance in the absence of a historical genotype and achieved HIV-1 RNA reduction to 70 copies/mL with continued E/C/F/TAF treatment prior to switching to a new regimen.
- The fourth subject tested was found to have no resistance to any study drug.