FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Randomized, Open-Label Study to Evaluate Switching from a Tenofovir Disoproxil Fumarate (TDF) Containing Regimen to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 60 Years
Name of Test Drug:	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF [E/C/F/TAF]; Genvoya® [GEN])
Dose and Formulation:	Fixed-dose combination tablet of E/C/F/TAF (150/150/200/10 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-292-1826
Phase of Development:	Phase 3b
IND No.: **EudraCT No.:**	111007 2015-002712-32
ClinicalTrials.gov Identifier:	NCT02616783
Study Start Date:	22 December 2015 (First Subject Screened)
Study End Date:	21 March 2018 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Franco Maggiolo, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Richard Haubrich, MD Telephone: PPD Fax: PPD
Report Date:	20 August 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-292-1826
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b, Randomized, Open-Label Study to Evaluate Switching from a Tenofovir Disoproxil Fumarate (TDF) Containing Regimen to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed, HIV-1 Infected Subjects Aged ≥ 60 Years

Investigators: Multicenter study

Study Centers: 11 sites in France, 9 sites in Italy, 11 sites in Spain, 3 sites in the United Kingdom, and 2 sites in Belgium

Publications: There were no publications based on the study at the time of this clinical study report (CSR).

Study Period:

22 December 2015 (First Subject Screened)
21 March 2018 (Last Subject Last Observation for the Primary Endpoint)

Phase of Development: Phase 3b

Objectives:

The primary objective of this study was as follows:

- To evaluate the safety of GEN relative to unchanged current antiretroviral therapy (ART) by assessing spine and hip bone mineral density (BMD) measured at Week 48 in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years

The secondary objectives of this study were as follows:

- To evaluate spine and hip BMD at Week 24
- To evaluate maintenance of HIV-1 RNA suppression < 50 copies/mL between regimens at Weeks 24 and 48
- To evaluate the safety and tolerability of the 2 treatment groups through Week 48

Methodology: This was a randomized, open-label, multicenter, active-controlled study to evaluate switching to GEN from a TDF and FTC- or 3TC-containing backbone regimen (maximum of 2 NRTIs), plus a third agent in virologically-suppressed, HIV-1 infected subjects aged ≥ 60 years.

Subjects were randomized in a 2:1 ratio to one of the following treatment groups:

- **Treatment Group 1:** Switch to GEN from TDF+FTC+3rd agent or TDF+3TC+3rd agent (n = 100)
- **Treatment Group 2:** Remain on TDF+FTC+3rd agent or TDF+3TC+3rd agent (stay on baseline regimen [SBR]) (n = 50)

Randomization was stratified based on a bivariate cut-point of the screening spine and hip BMD T-score < −1.00 or ≥ −1.00.

After screening, study visits occurred at Day 1 and Weeks 4, 8, 12, 24, 36, and 48.

Laboratory analyses (chemistry, hematology, and urinalysis), HIV-1 RNA, CD4 cell count, assessment of adverse events and concomitant medications, vital signs and weight measurements, and complete or symptom-directed physical examinations were performed at all study visits.

Blood and urine samples for selected evaluations of bone and renal safety, inflammation, and platelet and coagulation function were collected at Day 1 and Weeks 4, 12, 24, and 48.

Dual-energy x-ray absorptiometry (DXA) scans were performed at screening, and Weeks 24 and 48. Scans covered the spine and hip to measure changes in BMD.

Number of Subjects (Planned and Analyzed):
Planned: 150 subjects
Analyzed: 166 subjects (GEN: 110 subjects; SBR: 56 subjects)
Analyzed (by analysis set):

	GEN	SBR
Subjects in Safety Analysis Set	110	56
Subjects in Full Analysis Set (FAS)	109	55
Subjects in Spine DXA Analysis Set	109	55
Subjects in Hip DXA Analysis Set	109	55

Diagnosis and Main Criteria for Inclusion: Subjects enrolled received TDF+FTC+3rd agent or TDF+3TC+3rd agent for ≥ 6 consecutive months preceding the screening visit. For subjects with 3 or more ART regimens, a regimen history was provided for approval by the sponsor. Allowed third agents included: LPV/r, ATV+RTV, ATV+COBI (or ATV/COBI FDC), DRV+RTV, DRV+COBI (or DRV/COBI FDC), FPV+RTV, SQV+RTV, EFV, RPV, NVP, ETR, RAL, EVG+COBI, or DTG.

Subjects had to have documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay) and plasma HIV-1 RNA < 50 copies/mL at screening. In the preceding 6 months prior to screening, 1 episode of HIV-1 RNA between > 50 and < 400 copies/mL was acceptable, only if HIV-1 RNA was < 50 copies/mL immediately before and after the episode.

In addition, subjects had to have documented historical plasma genotypes that did not show resistance to TDF or FTC, including, but not limited to the presence of reverse transcriptase resistance mutants K65R, K70E, M184V/I, or thymidine analog-associated mutations (TAMs) (TAMs were: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R). If historical plasma genotype prior to first ART was not available or the subject had 3 or more ART regimens, the subject had proviral genotype analysis prior to Day 1 to confirm absence of archived resistance to TDF or FTC.

Duration of Treatment: A 42-day screening period followed by 48 weeks on study and a 30-day follow-up visit after completion of study

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

Batch numbers: CP1502B1, CP1505B1, CP1604B1, CP1605B1

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

TDF+FTC+3rd agent or TDF+3TC+3rd agent administered orally

Investigators provided a prescription for the treatment, and subjects were responsible for obtaining their medication prior to or during the study visit.

Criteria for Evaluation:

Efficacy: Plasma HIV-1 RNA and CD4 cell count were assessed at Day 1; Weeks 4, 8, 12, 24, 36, and 48; and the 30-day follow-up visit.

Pharmacokinetics/Pharmacodynamics: No pharmacokinetics (PK)/pharmacodynamics (PD) assessments were performed for this report.

Safety: Safety assessments included monitoring of adverse events (AEs) (including fracture events) and concomitant medications, clinical laboratory analyses, DXA scans, vital signs measurements, electrocardiograms (ECGs), and physical examinations. Clinical laboratory analyses included bone biomarkers (parathyroid [PTH] and serum OH-25 vitamin D), serum creatinine, $eGFR_{CG}$, proteinuria (dipstick), renal biomarkers (eg, urine protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR], urine retinol binding protein [RBP] to creatinine ratio, and beta-2-microglobulin to creatinine ratio), metabolic assessments, testosterone, markers of inflammation, and markers of platelet and coagulation function.

Other: Patient reported outcome (PRO)-related questionnaires included the Visual Analogue Scale (VAS), HIV Treatment Satisfaction (HIVTSQs and HIVTSQc versions), EQ-5D-3L, Medical Outcome Study Short Form-36 (SF-36), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).

Statistical Methods:

Efficacy: The Full Analysis Set (FAS) included all subjects who were randomized, received at least 1 dose of study drug, and did not have any major protocol violations. Efficacy analyses were conducted using the FAS.

The proportions of subjects with HIV-1 RNA < 50 copies/mL and ≥ 50 copies/mL at Weeks 24 and 48, as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm, and the changes from baseline in CD4 cell count at Weeks 24 and 48 were secondary endpoints in this study. Other efficacy endpoints included the proportions of subjects with HIV-1 RNA < 20 copies/mL at Weeks 24 and 48, as determined by the US FDA-defined snapshot algorithm, the proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as determined using 2 different missing data imputation methods, and the changes from baseline in CD4% at Weeks 24 and 48.

For differences between treatment groups in the proportions of subjects with HIV-1 RNA < 50 copies/mL and in the proportions of subjects with HIV-1 RNA ≥ 50 copies/mL at Weeks 24 and 48 as determined using the US FDA-defined snapshot algorithm, the 2-sided exact 95% CIs for the differences in treatment group response rates (E/C/F/TAF − SBR) were constructed using 2 inverted 1-sided tests. P-values were calculated for the proportions of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using Fisher's exact test. The differences between treatment groups in the proportions of subjects with HIV-1 RNA < 20 copies/mL at Weeks 24 and 48 as determined using the US FDA-defined snapshot algorithm were similarly analyzed.

The differences between treatment groups in the proportions of subjects with HIV-1 RNA < 50 copies/mL as determined using missing = failure (M = F) and missing = excluded (M = E) analyses used the same statistical methods used for analyzing the proportions of subjects with HIV-1 RNA < 50 copies/mL as determined using the US FDA-defined snapshot algorithm. In addition, the 95% CI of the proportions of subjects with HIV-1 RNA < 50 copies/mL within each treatment group were calculated using the Clopper-Pearson exact method.

For the differences between treatment groups in CD4 cell count at Weeks 24 and 48, the 95% CIs were constructed and p-values generated using analysis of variance (ANOVA) models including treatment as a fixed effect. The differences between treatment groups in CD4% at Weeks 24 and 48 were similarly analyzed.

Pharmacokinetics/Pharmacodynamics: No PK/PD assessments were performed for this report.

Safety: The primary endpoints of the study were the percentage changes from baseline in spine BMD and hip BMD at Week 48. The Spine and Hip DXA Analysis Sets included all subjects who were randomized into the study, received at least 1 dose of study drug, had nonmissing screening spine or hip BMD values, respectively, and did not have any major protocol violations.

The percentage changes from baseline in spine and hip BMD at Week 48 were summarized by treatment group and visit using descriptive statistics for subjects in the Spine and Hip DXA Analysis Sets. The percentage changes from baseline in spine and hip BMD were compared between the 2 treatment groups using an ANOVA model, including treatment group, baseline BMD T-score (< −1.00 vs ≥ −1.00), and sex as fixed effects in the model. Multiplicity adjustments were performed using a fallback procedure. As a sensitivity analysis of the primary endpoint, missing values were imputed using last observation carried forward (LOCF) imputation for analyses of the differences between treatment groups in percentage changes from baseline in spine and hip BMD.

Secondary endpoints were the percentage changes from baseline in spine BMD and hip BMD at Week 24. The percentage changes from baseline in spine BMD and hip BMD at Week 24 were analyzed using the same methods as the percentage changes from baseline in spine BMD and hip BMD at Week 48.

The Safety Analysis Set included all subjects who were randomized into the study and received at least 1 dose of study drug. The Safety Analysis Set was the primary analysis set for safety analyses.

Safety data were summarized for the subjects in the Safety Analysis Set. All safety data collected up to 30 days after permanent discontinuation of study drug were summarized by treatment group, unless specified otherwise in the SAP. Descriptive statistics were provided for AEs and clinical laboratory data by treatment group.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1.

Laboratory data collected during the study were analyzed and summarized using descriptive statistics.

All safety data were included in data listings (Appendix 16.2).

Other: Patient-reported outcome data collected during the study were analyzed and summarized using descriptive statistics. Summaries were provided for the Safety Analysis Set. Unless otherwise stated, multiple responses and out of range responses were set to missing, and missing responses were not imputed. All reported data were included in data listings (Appendix 16.2).

SUMMARY OF RESULTS:

Subject Disposition:

A total of 167 subjects were randomized, of which 166 subjects received at least 1 dose of the study drug (GEN 110 subjects; SBR 56 subjects); 1 subject randomized to the GEN group did not receive study drug. A total of 102 subjects in the GEN group and 53 subjects in the SBR group completed 48 weeks of treatment.

Subjects who prematurely discontinued study drug were as follows: GEN 8 of 110 subjects (7.3%); SBR 3 of 56 subjects (5.4%). Reasons for premature discontinuation of study drug in the GEN group were as follows: AE (4 subjects), and noncompliance with study drug, protocol violation, subject decision, or death (1 subject each). Reasons for study drug discontinuation in the SBR group were as follows: AE, protocol violation, and subject decision (1 subject each) (Table 15.8.1.3).

Subject Demographics and Baseline Characteristics:

Demographics and general baseline characteristics were similar between the 2 treatment groups (Safety Analysis Set) (Table 15.8.3.3).

Overall, the majority of subjects were male (GEN 87.3%; SBR 91.1%), with a mean age as follows: GEN 65 years (range 60 to 80); SBR 66 years (range 60 to 80). Most subjects were white (GEN 93.6%; SBR 87.5%) and not Hispanic or Latino (GEN 80.0%; SBR 75.0%). The mean (SD) baseline values for body mass index were as follows: GEN 26.3 (4.01) kg/m^2; SBR 25.8 (3.93) kg/m^2 (Table 15.8.3.1).

In the GEN group, most subjects had baseline HIV-1 RNA < 50 copies/mL (109 of 110 subjects; 99.1%); 1 of 110 subjects (0.9%) had HIV-1 RNA ≥ 50 copies/mL. The mean (SD) CD4 cell count was 649 (255.6) cells/μL. The most common HIV risk factor category was homosexual sex (47.3%); 43.6% of subjects had heterosexual sex as an HIV risk factor. Four subjects (3.6%) were positive for hepatitis B virus surface antigen (HBsAg), and 11 subjects (10.0%) were positive for hepatitis C virus (HCV) antibody. The majority of subjects had no proteinuria as assessed by dipstick (52.7%). Mean (SD) $eGFR_{CG}$ was 82.7 (21.34) mL/min. Most subjects did not have a history of diabetes mellitus (84.5%), hypertension (60.9%), cardiovascular disease (96.4%), hyperlipidemia (72.7%), or familial history (mother/father/brother/sister) of myocardial infarction or stroke before the age of 50 years (80.9%).

In the SBR group, all subjects had baseline HIV-1 RNA < 50 copies/mL. The mean (SD) CD4 cell count was 676 (316.5) cells/μL. The most common HIV risk factor category was heterosexual sex (57.1%); 33.9% of subjects had homosexual sex as an HIV risk factor. Two subjects (3.6%) were positive for HBsAg, and 4 subjects (7.1%) were positive for HCV antibody. Twenty-eight subjects (50.0%) had no proteinuria as assessed by dipstick. The mean (SD) $eGFR_{CG}$ value was 79.0 (15.96) mL/min. Most subjects did not have a history of diabetes mellitus (89.3%), hypertension (71.4%), cardiovascular disease (98.2%), hyperlipidemia (73.2%), or familial history (mother/father/brother/sister) of myocardial infarction or stroke before the age of 50 years (89.3%).

Primary Endpoint Results:

Spine and Hip BMD

The primary endpoint of this study was the percentage changes from baseline in spine BMD and hip BMD at Week 48. For subjects who switched to GEN, there were mean increases from baseline in both spine BMD and hip BMD through Week 48, compared with decreases in both parameters in the SBR group (Tables 15.11.7.4.1.1 and 15.11.7.4.1.3). The differences between subjects who switched to GEN and subjects who remained on their baseline regimen (SBR) with respect to both spine BMD and hip BMD were statistically significant at Week 48 ($p < 0.001$ for both parameters). Mean (SD) percentage changes from baseline in spine BMD and hip BMD at Week 48 (observed data) were as follows:

- **Spine:** GEN: 2.237% (3.2727%); SBR: −0.104% (3.3854%); difference in percentages: 2.427%, 95% CI: 1.337%, 3.517%
- **Hip:** GEN: 1.330% (2.1968%); SBR: −0.726% (3.2069%); difference in percentages: 2.036%, 95% CI: 1.168%, 2.904%

Similar to results at Week 48, mean increases from baseline in both spine BMD and hip BMD in the GEN group and decreases in both parameters in the SBR group were observed at Week 24, as follows:

- **Spine:** GEN: 1.625% (3.2346%); SBR: −0.027% (2.9875%); difference in percentages: 1.749%, 95% CI: 0.726%, 2.771%
- **Hip:** GEN: 0.808% (1.9084%); SBR: −0.537% (2.7647%); difference in percentages: 1.351%, 95% CI: 0.602%, 2.099%

The differences between subjects who switched to GEN and subjects who remained on their baseline regimen (SBR) with respect to both spine BMD and hip BMD at Week 24 were statistically significant ($p < 0.001$ for both parameters).

Results using LOCF analysis were similar to results using observed data at Weeks 24 and 48 (Tables 15.11.7.4.1.2 and 15.11.7.4.1.4).

Spine and Hip BMD Clinical Status

The majority of subjects in both treatment groups had normal spine and hip BMD clinical status at baseline, and that status was retained at Weeks 24 and 48 (Tables 15.11.7.4.2 and 15.11.7.4.3). There were no statistically significant differences between groups in the distribution of spine BMD clinical status, adjusted for baseline spine BMD clinical status, at Weeks 24 or 48. The differences between groups in the distribution of hip BMD clinical status, adjusted for baseline hip BMD clinical status, were statistically significant at Weeks 24 ($p = 0.026$) and 48 ($p = 0.001$). Of subjects with normal hip BMD clinical status or osteopenia at baseline who had hip BMD data at Week 24, 1 of 101 subjects (1.0%) in the GEN group and 4 of 53 subjects (7.5%) in the SBR group had worsening hip BMD clinical status. Of subjects with hip osteopenia or osteoporosis at baseline who had hip BMD data at Week 24, 7 of 52 subjects (13.5%) in the GEN group and 1 of 26 subjects (3.8%) in the SBR group had improvements in hip BMD clinical status. Of subjects with normal hip BMD clinical status or osteopenia at baseline who had hip BMD data at Week 48, no subject in the GEN group and 4 of 53 subjects (7.5%) in the SBR group had worsening hip BMD clinical status. Of subjects with hip osteopenia or osteoporosis at baseline who had hip BMD data at Week 48, 8 of 50 subjects (16.0%) in the GEN group and no subject in the SBR group had improvements in hip BMD clinical status.

Categorical Distribution of Percentage Change from Baseline in BMD

At Week 48, higher percentages of subjects in the GEN group than the SBR group had a ≥ 3% increase in BMD at the spine (40.2% vs 22.2%) and hip (23.8% vs 3.7%), and lower percentages of subjects in the GEN group had a ≥ 3% decrease in BMD at the spine (4.9% vs 20.4%) and hip (3.0% vs 9.3%) (Tables 15.11.7.4.7 and 15.11.7.4.8).

The numbers of subjects with a decrease from baseline of ≥ 7% in BMD in the femoral neck at Week 48 were as follows: GEN 0 of 101 subjects; SBR 1 of 54 subjects, 1.9% (Table 15.11.7.4.9). The numbers of subjects with a decrease from baseline of ≥ 5% in BMD in the spine at Week 48 were as follows: GEN 2 of 102 subjects, 2.0%; SBR 4 of 54 subjects, 7.4% (Table 15.11.7.4.7).

Efficacy Results:

High rates of virologic suppression were maintained in both treatment groups at Weeks 24 and 48 (Tables 15.9.2.1 and 15.9.1.1). The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 24 as determined using the US FDA-defined snapshot algorithm were as follows: GEN 94.5% (103 of 109 subjects); SBR 100.0% (55 of 55 subjects); difference in percentages: −5.5%, 95% CI: −11.8% to 1.6%; $p = 0.18$. The percentages of subjects in the FAS with HIV 1 RNA < 50 copies/mL at Week 48 (US FDA-defined snapshot algorithm) were as follows: GEN 93.6% (102 of 109 subjects); SBR 94.5% (52 of 55 subjects); difference in percentages: −1.0%, 95% CI: −8.5% to 9.3%; $p = 1.00$. No subject in either treatment group had HIV-1 RNA ≥ 50 copies/mL at Week 24 (difference in percentages not calculable). One subject

in each treatment group had HIV-1 RNA ≥ 50 copies/mL at Week 48 (difference in percentages: −0.9%; 95% CI: −9.0% to 3.9%). Six subjects (5.5%) in the GEN group had no virologic data in the Week 24 and 48 windows (4 subjects [3.7%] discontinued study drug due to AE or death and last available HIV-1 RNA was < 50 copies/mL, and 2 subjects [1.8%] discontinued study drug due to other reasons and last available HIV-1 RNA was < 50 copies/mL). Two subjects (3.6%) in the SBR group had no virologic data in the Week 48 window (1 subject [1.8%] discontinued study drug due to AE or death and last available HIV-1 RNA was < 50 copies/mL, and 1 subject [1.8%] discontinued study drug due to other reasons and last available HIV-1 RNA was < 50 copies/mL)**.**

The percentages of subjects in the FAS with HIV-1 RNA < 20 copies/mL at Weeks 24 and 48 (US FDA-defined snapshot algorithm) are presented in Tables 15.9.3.2 and 15.9.3.1. The percentages of subjects in each treatment group with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as determined using the M = F and M = E methods are presented in Tables 15.9.3.3 and 15.9.3.4.

Mean (SD) baseline CD4 cell counts were as follows: GEN 649 (256.7) cells/μL; SBR 683 (314.9) cells/μL. In the GEN group, a gradual increase from baseline in mean CD4 cell count was observed from baseline to Week 12 (46 [208.7 cells/μL]) that remained stable through Week 24 (48 [161.9] cells/μL) and Week 48 (56 [177.7] cells/μL). In the SBR group, little change from baseline in mean CD4 cell counts was observed at Weeks 24 (−4 [153.9] cells/μL) or Week 48 (−1 [149.1] cells/μL) (Table 15.9.2.2). The difference between groups in changes from baseline in CD4 cell count (95% CI) at Week 48 was 57 (0, 115) cells/μL (p = 0.051).

Results for CD4% are presented in Table 15.9.3.5.

Of the 166 subjects who received study drug through Week 48, 2 subjects (1.2%) were analyzed for the development of HIV-1 drug resistance (1 subject in the GEN group and 1 subject in the SBR group). Both subjects had HIV-1 RNA > 50 copies/mL at their last visit at Week 48. No emerging resistance was detected, as resistance testing resulted in assay failure for both subjects (Virology Listings 3 and 4).

Pharmacokinetics/Pharmacodynamics Results:

No PK/PD assessments were performed for this report.

Safety Results:

Overall, GEN was generally well tolerated in this study. The median (Q1, Q3) exposures to study drugs were as follows: GEN 48.0 (47.6, 48.1) weeks; SBR 48.0 (47.8, 48.2) weeks (Table 15.11.1.1).

Adverse Events

Through Week 48, treatment-emergent AEs were reported in 87 of 110 subjects (79.1%) in the GEN group and 34 of 56 subjects (60.7%) in the SBR group (Table 15.11.2.1.1.1). Study drug-related AEs were reported in 22 subjects (20.0%) in the GEN group and 1 subject (1.8%) in the SBR group. Most reported AEs were Grade 1 or 2 in severity. Grade 3 or 4 AEs were reported in 9 subjects (8.2%) in the GEN group and 1 subject (1.8%) in the SBR group. No Grade 3 or 4 AE was considered related to study drug. Serious adverse events (SAEs) were reported in 10 subjects (9.1%) in the GEN group and 1 subject (1.8%) in the SBR group

(Table 15.11.4.1). No SAE was reported for more than 1 subject, and none of the SAEs were considered related to study drug. One treatment-emergent death occurred during the study in a subject in the GEN group. The immediate cause of death was Grade 4 sepsis that had an onset date 40 days after the subject was diagnosed with metastatic colorectal cancer (Listings 16.2.7.1 and 16.2.7.6). The Grade 4 sepsis was not considered related to study drug. Four subjects (3.6%) in the GEN group and 1 subject (1.8%) in the SBR group had an AE that led to premature discontinuation of study drug. The only AE leading to premature discontinuation of study drug that was reported for more than 1 subject was diarrhea (2 subjects [1.8%] in the GEN group) (Table 15.11.5).

The 3 most common AEs reported in each treatment group through Week 48 were as follows (Table 15.11.2.1.2.2):

- GEN: nasopharyngitis (12 of 110 subjects, 10.9%), back pain (9 subjects, 8.2%), and diarrhea (8 subjects, 7.3%)
- SBR: bronchitis (6 of 56 subjects, 10.7%), and arthralgia or vitamin D deficiency (4 subjects, 7.1% each)

The most common AEs considered related to study drug in the GEN group were diarrhea (5 of 110 subjects, 4.5%), and erectile dysfunction or headache (2 subjects, 1.8% each). Osteoporosis was the only AE considered related to study drug in the SBR group (1 subject, 1.8%) (Table 15.11.2.3.1.2).

An event that met the Stage 3 opportunistic illness definition of an AIDS-defining diagnosis (Kaposi's sarcoma) was reported for 1 subject in the SBR group (Listing 16.2.7.3).

Subject narratives for AEs that led to premature study drug discontinuation, SAEs, and deaths are provided in Section 15.2.

Bone Safety

Fracture Events

No treatment-emergent fracture events were reported (Table 15.11.2.4.2).

Bone Biomarkers

Through Week 48, similar median percentage changes from baseline in PTH and serum OH-25 vitamin D were observed in the GEN and SBR groups (Tables 15.11.6.6.1 and 15.11.6.6.2). At Week 48, the median (Q1, Q3) percentage changes from baseline in PTH were as follows: GEN −19.6% (−32.2%, −1.6%); SBR −13.5% (−35.5%, 15.3%). At Week 48, the median (Q1, Q3) percentage changes from baseline in OH-25 vitamin D were as follows: GEN −4.2% (−26.4%, 31.5%); SBR 3.7% (−17.8%, 37.1%).

Renal Safety

Renal Events

Through Week 48, no cases of proximal renal tubulopathy (including Fanconi syndrome) were reported in subjects who switched to GEN. A Grade 1 nonserious AE of renal tubular disorder was reported in 1 subject in the SBR group (Table 15.11.2.1.2.1). The event started on Day 29 and resolved on Day 37, and was not considered related to study drug (Listing 16.2.7.1).

No subject discontinued study drug due to a renal or urinary disorder or associated investigation AE (Table 15.11.5).

Through Week 48, renal and urinary disorders or associated investigation AEs reported in more than 1 subject in the GEN group were pollakiuria and urinary retention (2 of 110 subjects, 1.8% each) (Table 15.11.2.1.2.1). Hematuria, urinary retention, and acute kidney injury (1 subject, 0.9% each) were the only Grade 3 or 4 renal AEs (Table 15.11.2.2.2). Grade 4 acute kidney injury and an SAE of Grade 2 renal colic were the only renal and urinary disorders or associated investigation SAEs reported, and occurred in a single subject in the setting of E. coli sepsis (Table 15.11.4.1 and Listing 16.2.7.7). A Grade 1 AE of creatinine renal clearance decreased was considered related to study drug (Table 15.11.2.3.1.1 and Listing 16.2.7.1); this subject had normal urine beta-2-microglobulin to creatinine and urine RBP to creatinine ratios, and did not have proteinuria, glycosuria, or microalbuminuria (Listings 16.2.8.1.4.1, 16.2.8.1.4.5, and 16.2.8.1.4.6). No other Grade 3 or 4 renal AEs, renal SAEs, or renal AEs considered related to study drug were reported in subjects receiving GEN.

Through Week 48, the only renal and urinary disorder or associated investigation AE reported in more than 1 subject in the SBR group was dysuria (2 of 56 subjects, 3.6%) (Table 15.11.2.1.2.1). All renal and urinary disorders or associated investigation AEs reported in the SBR group were Grade 1 and nonserious, and none was considered related to study drug (Tables 15.11.2.2.1, 15.11.4.1, and 15.11.2.3.1.1).

Narratives for subjects with SAEs are provided in Section 15.2.

Serum Creatinine and $eGFR_{CG}$

Baseline median (Q1, Q3) serum creatinine values were GEN: 0.98 (0.86, 1.10) mg/dL; SBR: 1.01 (0.86, 1.11) mg/dL (Table 15.11.6.2.8). Little change from baseline in serum creatinine was seen in either group at Week 48 (GEN 0.00 [−0.09, 0.09] mg/dL; SBR −0.03 [−0.09, 0.04] mg/dL for median [Q1, Q3] changes from baseline at Week 48).

Baseline median (Q1, Q3) $eGFR_{CG}$ values were GEN: 80.4 (68.4, 92.4) mL/min; SBR: 79.8 (66.9, 87.9) mL/min (Table 15.11.6.2.9). At Week 48, a slight decrease from baseline was seen in the GEN group, with little change from baseline in the SBR group (GEN −2.4 [−7.2, 6.6] mL/min; SBR 0.6 [−5.7, 5.4] mL/min for median [Q1, Q3] changes from baseline at Week 48).

Proteinuria by Urinalysis (Dipstick)

At baseline, no subject had ≥ Grade 3 proteinuria, as assessed by dipstick analysis (Table 15.11.6.7.1). Four subjects in the GEN group and no subject in the SBR group had Grade 2 proteinuria, and 11 subjects in the GEN group and 8 subjects in the SBR group had Grade 1 proteinuria at baseline. At Week 48, 3 of the 4 subjects (75.0%) in the GEN group with Grade 2 proteinuria improved to Grade 1. In subjects with Grade 1 proteinuria at baseline, 10 of 11 subjects (90.0%) in the GEN group and 5 of 7 subjects (71.4%) in the SBR group improved to Grade 0, and 1 subject (9.1%) in the GEN group and no subject in the SBR group worsened to Grade 2 at Week 48. In subjects with no proteinuria at baseline, 6 of 88 subjects (6.8%) in the GEN group and 6 of 46 subjects (13.0%) in the SBR group worsened to Grade 1 proteinuria, and 1 subject (1.1%) in the GEN group and no subject in the SBR group worsened to Grade 2 proteinuria at Week 48.

Proteinuria by Quantitative Assessment

Decreases from baseline in UACR were seen through Week 48 in both treatment groups, with larger decreases in the GEN group compared with the SBR group (Table 15.11.6.7.2.2). At Week 48, median (Q1, Q3) percentage changes from baseline in UACR were GEN −27.8% (−56.6%, 4.7%); SBR −7.7% (−36.1%, 60.0%). Differences between the groups in median percentage changes from baseline in UACR at Week 48 were statistically significant ($p = 0.004$).

Similar decreases from baseline in UPCR were seen through Week 48, with larger decreases in the GEN group compared with the SBR group (Table 15.11.6.7.2.1). At Week 48, median (Q1, Q3) percentage changes from baseline in UPCR were GEN −49.8% (−66.1%, −6.8%); SBR −3.8% (−27.4%, 50.4%). Differences between the groups were statistically significant ($p < 0.001$ at Week 48).

Urine RBP to Creatinine Ratio and Beta-2-Microglobulin to Creatinine Ratio

Decreases from baseline in urine RBP to creatinine ratio were seen in the GEN group, with smaller decreases and an increase in the SBR group through Week 48 (Table 15.11.6.7.3.1). Median (Q1, Q3) percentage changes from baseline in urine RBP to creatinine ratio at Week 48 were GEN −41.5% (−67.9%, −7.7%); SBR 15.2% (−36.2%, 94.7%). Differences between the groups were statistically significant ($p < 0.001$ at Week 48).

Decreases from baseline in beta-2-microglobulin to creatinine ratio were seen in the GEN group, with mostly increases in the SBR group through Week 48 (Table 15.11.6.7.3.2). Median (Q1, Q3) percentage changes from baseline in beta-2-microglobulin to creatinine ratio at Week 48 were GEN −58.7% (−87.4%, −25.0%); SBR 13.6% (−24.5%, 151.9%). Differences between the groups were statistically significant ($p < 0.001$ at Week 48).

Cardiovascular and Cerebrovascular Safety

Cardiovascular or cerebrovascular events were reported in 5 of 110 subjects (4.5%) in the GEN group and 1 of 56 subjects (1.8%) in the SBR group (Table 15.11.2.4.1). Grade 3 or 4 cardiovascular or cerebrovascular events were Grade 3 acute coronary syndrome in a subject in the GEN group with a history of acute myocardial infarction; Grade 3 carotid artery stenosis in a subject in the GEN group with a history of coronary arterial bypass, diabetes, hypertension, and type 2 diabetes; and Grade 4 acute coronary syndrome in a subject in the SBR group with a history of dyslipidemia, hypertension, and moderate aortic stenosis (Listings 16.2.7.4 and 16.2.4.5). Each of the Grade 3 or 4 cardiovascular or cerebrovascular events were also SAEs. No other Grade 3 or 4 cardiovascular or cerebrovascular events, or cardiovascular or cerebrovascular events considered SAEs were reported. No cardiovascular or cerebrovascular event was considered related to study drug.

Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for hematology and clinical chemistry laboratory assessments in either treatment group through Week 48, and median values were within normal ranges (Tables 15.11.6.1.1 to 15.11.6.2.17.2).

Through Week 48, the majority of subjects in both treatment groups had at least 1 laboratory abnormality (GEN: 87 of 110 subjects, 79.1%; SBR: 46 of 56 subjects, 82.1%) (Table 15.11.6.4.1). Most of the reported laboratory abnormalities were Grade 1 or 2. The

percentages of subjects with Grade 3 or 4 laboratory abnormalities through Week 48 were as follows: GEN: 11.8%, 13 subjects; SBR: 12.5%, 7 subjects (Table 15.11.6.4.2). The only Grade 3 or higher laboratory abnormalities reported for ≥ 5% of subjects in either group were fasting LDL cholesterol increased (GEN: 9.6%, 10 subjects; SBR: 3.7%, 2 subjects) and glycosuria (GEN: 0.9%, 1 subject; SBR: 7.1%, 4 subjects). The only Grade 4 laboratory abnormality was hyponatremia reported in 1 subject in the GEN group.

Metabolic Laboratory Abnormalities

Increases in median lipid parameter values were seen through Week 48 in the GEN group, with decreases or smaller increases in the SBR group (Tables 15.11.6.3.1 to 15.11.6.3.5). Differences between the 2 groups in changes from baseline in fasting values at Week 48 were statistically significant for total cholesterol, direct LDL cholesterol, total cholesterol to HDL ratio, and triglycerides ($p < 0.001$ for each parameter). The differences between groups were not clinically relevant. Results were similar when subjects taking lipid modifying medications were excluded (Tables 15.11.6.3.9 to 15.11.6.3.13).

The majority of lipid laboratory abnormalities reported through Week 48 were Grade 1 or 2 (Table 15.11.6.4.1). Grade 3 hypercholesterolemia was reported in 4 subjects (3.8%) in the GEN group and no subject in the SBR group. Grade 3 increased LDL was reported in 10 subjects (9.6%) in the GEN group and 2 subjects (3.7%) in the SBR group.

Little change from baseline in median value for fasting glucose was seen in either group at Week 48 (Table 15.11.6.3.6).

Other Safety Results

There were no clinically relevant changes in vital signs, body weight, or ECG readings in either treatment group during the study (Tables 15.11.7.1.1 to 15.11.7.2, and Table 15.11.8).

Patient-Reported Outcome Results:

There were no differences between treatment groups in any PRO assessment through Week 48 (Tables 15.12.1.1 to 15.12.5.4).

CONCLUSIONS:

The conclusions from this study are as follows:

- Spine and hip BMD increased from baseline through Week 48 in those who switched to GEN, and decreased from baseline in those who continued their baseline regimen. Differences between the 2 groups were statistically significant at Weeks 24 and 48.
- High rates of virologic suppression were maintained in both treatment groups through 48 weeks of treatment. The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 (US FDA-defined snapshot algorithm) were GEN 93.6%; SBR 94.5%; difference in percentages: −1.0%, 95% CI: −8.5% to 9.3%.
- No virologic resistance to study drug emerged through Week 48.
- GEN was well tolerated as demonstrated by the low incidence of SAEs and AEs leading to discontinuation of study drug. None of the reported SAEs were study drug related. Adverse events were consistent with the safety profile of GEN.

- No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported in subjects who switched to GEN, and no renal and urinary disorder or associated investigation AE led to discontinuation of study drug.
- Little change from baseline in serum creatinine or $eGFR_{CG}$ was observed in either treatment group at Week 48.
- Decreases from baseline in renal biomarkers (proteinuria by quantitative assessments, urine RBP to creatinine ratio, and beta-2-microglobulin to creatinine ratio) were seen after switching to GEN, compared with smaller decreases or increases in those who continued their baseline regimen.
- Changes in fasting lipid parameters and total cholesterol to HDL ratio after switching to GEN were not clinically relevant.

The Week 48 BMD, safety, and efficacy data from this study support switching to GEN from a TDF-containing regimen in virologically suppressed HIV-infected patients aged > 60 years.