FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naive Adults
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-292-0104
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	111007 2012-004458-27
ClinicalTrials.gov Identifier:	NCT01780506
Study Start Date:	26 December 2012 (First Subject Screened)
Study End Date:	06 September 2017 (Last Subject Last Observation)
Principal or Coordinating Investigator:	Name: Paul Edward Sax, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Sean Collins, MD, MS Telephone: PPD Fax: PPD
Report Date:	15 February 2018
Previous Report Dates:	21 September 2016 (Week 144 Clinical Study Report) 02 October 2015 (Week 96 Clinical Study Report) 06 October 2014 (Week 48 Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-292-0104

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

Title of Study: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Versus Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment-Naive Adults

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled in a total of 120 study centers: 82 in the United States (US), 9 in Spain, 8 in Canada, 6 in Thailand, 5 in Australia, 3 in Switzerland, 2 in Austria, 2 in Belgium, 1 in Italy, 1 in Japan, and 1 in the United Kingdom.

Publications:

Arribas JR, Thompson M, Sax PE, Haas B, McDonald C, Wohl DA, et al. Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated with Elvitegravir, Cobicistat and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. J Acquire Immune Defic Syndr. 2017;75(2):211-218.

Margot N, Cox S, Das M, McCallister S, Miller MD, Callebaut C. Infrequent development of drug resistance in HIV-1-infected treatment-naive subjects after 96 weeks of treatment with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. Antivir Ther. 2017;22(5):443-446.

Margot NA, Kitrinos KM, Fordyce M, McCallister S, Miller MD, Callebaut C. Rare emergence of drug resistance in HIV-1 treatment-naïve patients after 48 weeks of treatment with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. HIV Clin Trials. 2016 Mar;17(2):78-87.

Funderburg NT, McComsey GA, Kulkarni M, Bannerman T, Mantini J, Thornton B. Equivalent Decline in Inflammation Markers with Tenofovir Disoproxil Fumarate vs. Tenofovir Alafenamide. EBioMedicine. 2016;13:321-327.

Wohl D, Oka S, Clumeck N, Clarke A, Brinson C, Stephens J, et al. Brief Report: A Randomized, Double-Blind Comparison of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate, Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine for Initial HIV-1 Treatment: Week 96 Results. J Acquir Immune Defic Syndr. 2016;72(1):58-64

Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate, Coformulated with Elvitegravir, Cobicistat, and Emtricitabine, for Initial Treatment of HIV-1 Infection: Two Randomized, Double-Blind, Phase 3, Non-Inferiority Trials. Lancet 2015; 385 (9987): 2606-15.

Custodio JM, Garner W, Callebaut C, Fordyce M, Plummer A, Zhong L, et al. The Pharmacokinetics of Tenofovir and Tenofovir Diphosphate Following Administration of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate [Oral Abstract #6]. The 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. Washington DC, USA, May 26-28, 2015.

Study Period:

26 December 2012 (First Subject Screened)
06 September 2017 (Last Subject Last Observation)

Phase of Development: Phase 3

Objectives: Study GS-US-292-0104 was conducted to evaluate the efficacy and safety of a fixed-dose combination (FDC) tablet containing elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (E/C/F/TAF; Genvoya®; hereafter referred to as "GEN") versus an FDC tablet containing E/C/F/tenofovir disoproxil fumarate (TDF) (Stribild®; STB) in HIV-infected, antiretroviral therapy (ART)-naive adult subjects.

The primary objective of this study was as follows:

- To evaluate the efficacy of an FDC tablet containing GEN versus STB in HIV-infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objectives of this study were as follows:

- To determine the safety of the 2 treatment regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) at Week 48
- To determine the safety of the 2 treatment regimens as determined by the change from baseline in serum creatinine at Week 48
- To evaluate the safety and tolerability of the 2 treatment regimens through Week 48
- To evaluate the efficacy, durability, safety and tolerability of the 2 treatment regimens through Week 144

The primary objective and key secondary objectives were addressed in the Week 48 and Week 96 interim clinical study reports (CSRs) and are not addressed further in this report. The remaining secondary objectives were addressed in the Week 144 CSR. The current report describes available efficacy and safety data through the end of the study.

The designation "E/C/F/TAF" is used in preprogrammed tables, figures, and listings.

Methodology: This was a randomized, double-blind, multicenter, active-controlled study that evaluated the efficacy and safety of GEN versus STB in HIV-infected, ART-naive adult subjects.

Subjects were randomized in a 1:1 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 = 420)

Treatment Group 2: FDC tablet of STB (E/C/F/TDF, 150/150/200/300 mg) + placebo-to-match GEN once daily (n = 420)

Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 to ≤ 400,000 copies/mL, or > 400,000 copies/mL), CD4 count (< 50 cells/μL, 50 to 199 cells/μL, or ≥ 200 cells/μL), and region (US versus ex-US) at screening.

After Week 144, subjects continued to take their blinded study drug and attended visits every 12 weeks until treatment assignments were unblinded, at which point all subjects returned for an unblinding visit and were given the option to receive open-label (OL) GEN until GEN became commercially available, or until Gilead Sciences terminated the study in that country as defined in the protocol (Appendix 16.1.1).

Number of Subjects (Planned and Analyzed):

Planned: 840 subjects total (420 subjects in each treatment group)

Analyzed (by analysis set):

Analyzed in the Double-Blind Phase analysis (by analysis set):

	GEN	STB	Total
Subjects Randomized	438	434	872
Subjects in Safety Analysis Set	435 (99.3%)	432 (99.5%)	867 (99.4%)
Subjects in Full Analysis Set (FAS)	435 (99.3%)	432 (99.5%)	867 (99.4%)
Subjects in Hip DXA Analysis Set	424 (96.8%)	424 (97.7%)	848 (97.2%)
Subjects in Spine DXA Analysis Set	427 (97.5%)	425 (97.9%)	852 (97.7%)

DXA = dual-energy x-ray absorptiometry
The denominator for percentages is based on the number of subjects in the Randomized Analysis Set.
Source: Section 15.1, Table 2.1

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

	GEN	STB→GEN
Subjects in All GEN Analysis Set	435	94
Subjects in All GEN Hip DXA Analysis Set	424 (97.5%)	94 (100.0%)
Subjects in All GEN Spine DXA Analysis Set	427 (98.2%)	94 (100.0%)

The denominator for percentages is based on the number of subjects in the All GEN Analysis Set.
Source: Section 15.1, Table 2.2

Diagnosis and Main Criteria for Inclusion: Eligible subjects were ART-naive (excluding pre-exposure prophylaxis [PrEP] or postexposure prophylaxis [PEP] up to 6 months prior to screening), HIV-infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL, a screening genotype showing sensitivity to EVG, FTC, and tenofovir, and had an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault method ($eGFR_{CG}$) ≥ 50 mL/min.

Duration of Treatment: 144 weeks of randomized, double-blind treatment, followed by optional OL Extension Phase in which all subjects received GEN

Test Product, Dose, Mode of Administration, and Batch No.: FDC tablet of GEN (E/C/F/TAF, 150/150/200/10 mg), plus placebo-to-match STB, each administered orally once daily with food at approximately the same time.

Batch Numbers:

GEN: CP1204B1, CP1208B1, CP1209B1, CP1303B1, CP1307B1, CP1308B1, CP1311B1, CP1313B1, CP1314B1, CP1402B1, CP1403B1, CP1405B1, CP1502B1, CP1504B1, CP1506B1, CP1604B1, and CP1603B1

Placebo-to-match STB: BK1202B1, BK1206B1R, BK1301B1, BK1302B1, BK1205B1R, BK1402B1, and BK1403B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: FDC tablet of STB (E/C/F/TDF, 150/150/200/300 mg), plus placebo-to-match GEN, each administered orally once daily with food at approximately the same time.

Batch Numbers:

STB: BK1201B1, BK1203B1, BK1204B1, BK1304B1, BK1303B1, and BK1401B1

Placebo-to-match GEN: CP1206B1, CP1207B1, CP1309B1, CP1316B1, CP1317B1, CP1404B1, and CP1409B1

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the proportion of subjects that achieve HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US Food and Drug Administration (FDA)-defined snapshot algorithm. Results for the primary efficacy endpoint were described in the Week 48 and Week 96 interim CSRs. Results for secondary efficacy endpoints at Weeks 48, 96, and 144 were described in the Week 48, Week 96, and Week 144 interim CSRs.

Efficacy endpoints evaluated for the final analysis included the proportion of subjects with HIV-1 RNA < 50 copies/mL at each visit as defined by 2 different missing data imputation methods and change from baseline in CD4 cell count at each visit.

Pharmacokinetics: No pharmacokinetic (PK) analyses were performed for this report. All intensive PK analyses were described in the Week 48 interim CSR.

Safety: Safety assessments included adverse events (AEs), BMD using dual-energy x-ray absorptiometry (DXA), and clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy testing), including serum creatinine, $eGFR_{CG}$, proteinuria by quantitative assessment (urine protein to creatinine ratio [UPCR]), tubular proteinuria (urine retinol binding protein (RBP) to creatinine ratio and urine beta-2-microglobulin to creatinine ratio), and the bone biomarker parathyroid hormone (PTH).

Results for other renal biomarkers, including 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 described in the Week 48, Week 96, and Week 144 interim CSRs, as were bone biomarkers, including type 1 collagen C-telopeptide (C-telopeptide) and procollagen type 1 N-terminal propeptide (P1NP).

Other: Results for the EQ-5D-3L health-outcomes questionnaire were described in the Week 48 and Week 96 interim CSRs. Healthcare utilization, including the number of hospitalizations, unplanned visits for a healthcare issue, and unplanned specialty care provider visits for a healthcare issue, was described in the Week 48, Week 96, and Week 144 interim CSRs.

Statistical Methods: Documentation of statistical methods is provided in Appendix 16.1.9.

Efficacy: The efficacy analyses used the Full Analysis Set (FAS), which included all subjects who (1) were randomized into the study and (2) received at least 1 dose of study medication. Certain efficacy analyses used the All GEN Analysis Set, which included all subjects who were randomized and received at least 1 dose of double-blinded GEN during the Double-Blind Phase or OL GEN during the OL Extension Phase.

Virologic response, defined as achieving HIV-1 RNA < 50 copies/mL was analyzed using the following 2 methods for imputing missing HIV-1 RNA values: Missing = Failure (M = F) and Missing = Excluded (M = E).The changes from baseline in CD4 cell count at each visit were summarized by treatment group using descriptive statistics based on observed data using the FAS and All GEN Analysis Set, respectively.

Pharmacokinetics: No PK analyses were performed for this report.

Safety: Safety data were summarized by treatment group using descriptive statistics for the subjects in the Safety Analysis Set for the Double-Blind Phase analysis and for the All GEN Analysis Set for the all GEN analysis, unless otherwise specified. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. All safety data collected during the study were listed.

For the all GEN analysis, the baseline value was defined as the last nonmissing value obtained on or prior to Study Day 1 of the OL Extension Phase for subjects who switched to OL GEN from STB.

Because substantial long-term safety data were presented in the Week 144 interim CSR and this final analysis would only provide an additional 12 weeks of data for the Double-Blind Phase, the following safety analyses that were performed in the interim analyses were not performed for this final analysis:

- Categorical distribution of percentage change from baseline in hip or spine BMD
- Fracture events
- Potential cardiovascular and cerebrovascular events

SUMMARY OF RESULTS: All tables, figures, and listings produced for this study are provided in Section 15.1 (tables and figures) and Appendix 16.2 (listings).

Subject Disposition: A total of 867 subjects were randomized and received at least 1 dose of study drug in the Double-Blind Phase (GEN 435 subjects; STB 432 subjects; Section 15.1, Table 1). Of the 867 randomized and treated subjects, 712 subjects (GEN 83.9%, 365 subjects; STB 80.3%, 347 subjects) completed study drug in the Double-Blind Phase and 185 subjects (GEN 20.7%, 90 subjects; STB 22.0%, 95 subjects) entered the OL Extension Phase. Of the 185 subjects who entered the OL Extension Phase, 184 (GEN 90 subjects; STB 94 subjects) received at least 1 dose of OL GEN.

A total of 155 subjects (GEN 16.1%, 70 subjects; STB 19.7%, 85 subjects) discontinued study drug in the Double-Blind Phase. The most common reasons for premature discontinuation of study drug during the Double-Blind Phase were withdrawal of consent (GEN 4.6%, 20 subjects; STB 5.8%, 25 subjects), lost to follow up (GEN 4.8%, 21 subjects; STB 5.3%, 23 subjects), and AE (GEN 1.4%, 6 subjects; STB 4.6%, 20 subjects). A total of 8 subjects (GEN 4.4%, 4 subjects; STB→GEN 4.3%, 4 subjects) discontinued study drug in the OL Extension Phase. The reasons for premature discontinuation of study drug during the OL Extension Phase were withdrawal of consent (GEN 1.1%, 1 subject; STB→GEN 2.1%, 2 subjects) and lost to follow up (GEN 3.3%, 3 subjects; STB→GEN 2.1%, 2 subjects).

Subject Demographics and Baseline Disease Characteristics: Demographic and baseline characteristics were similar between the 2 treatment groups in the Double-Blind Phase (Section 15.1, Table 3.1). The majority of subjects in the Safety Analysis Set were male (85.4% overall). The median age was as follows: GEN 33 years (range: 18 to 74); STB 35 years (range: 18 to 76; p = 0.014). The most common races were white (58.2%), black (20.2%), and Asian (17.6%), and most subjects were not Hispanic or Latino (85.0%). Median (Q1, Q3) baseline body mass index was 24.3 (21.7, 27.7) kg/m^2.

Baseline disease characteristics were generally similar between the 2 treatment groups in the Double-Blind Phase (Section 15.1, Table 4.1). Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.61 (4.16, 4.97) log_{10} copies/mL. At baseline, 76.9% of subjects had HIV-1 RNA ≤ 100,000 copies/mL, 17.4% had > 100,000 to ≤ 400,000 copies/mL, and 5.7% had > 400,000 copies/mL. Overall, the median (Q1, Q3) baseline CD4 count was 404 (289, 554) cells/µL. At baseline, 2.5% (22 subjects) had a CD4 cell count < 50 cells/µL and 10.3% (89 subjects) had 50 to < 200 cells/µL. The most common HIV risk factor category was homosexual sex (74.7% of subjects). Few subjects (4.4%) had symptomatic HIV-1 infection, and 2.2% were diagnosed with AIDS.

At baseline, the median (Q1, Q3) $eGFR_{CG}$ value was higher in the GEN group (118.5 [101.6, 135.7] mL/min) compared with the STB group (112.8 [97.8, 134.2] mL/min) (p = 0.032).

The demographic and baseline characteristics of the All GEN Analysis Set were similar to those of the Safety Analysis Set (Section 15.1, Table 3.2).

Efficacy Results:

ART-Naive Subjects

Results for the proportion of subjects that achieved HIV 1 RNA < 50 copies/mL at Week 48, Week 96, and Week 144 as defined by the US FDA-defined snapshot algorithm were described in the Week 48, Week 96, and Week 144 interim CSRs.

Using the M = F and/or M = E methods, high rates of virologic suppression (defined as HIV-1 RNA < 50 copies/mL) were achieved and maintained in both treatment groups through the Double-Blind Phase based on the FAS, and were maintained in the GEN group through the OL Extension Phase based on the All GEN Analysis Set. The percentages of subjects with HIV-1 RNA < 50 copies/mL were as follows:

- M = F at Week 156 (Section 15.1, Table 8) GEN 85.3% (371 of 435 subjects); STB 84.7% (366 of 432 subjects); difference in percentages: 0.8%, 95% CI: −4.0% to 5.6%
- M = E at Week 168 (Section 15.1, Table 9.1) GEN 98.6% (286 of 290 subjects); STB 98.2% 274 of 279 subjects; difference in percentages: 0.5%, 95% CI: −2.0% to 2.9%
- M = E at Week 204 (Section 15.1, Table 9.2) GEN 92.7% (51 of 55 subjects)

Following initiation of study drug, CD4 cell counts increased in both treatment groups. Mean (SD) increases from baseline in CD4 cell counts at Week 168 of the Double-Blind Phase (observed data) using the FAS were as follows (Section 15.1, Table 10.1): GEN 342 (232.6) cells/µL; STB 349 (216.5) cells/µL; difference in least mean squares (LSM): −8 cells/µL, 95% CI: −47 to 31 cells/µL. The mean (SD) increase from baseline in CD4 cell count at Week 204 using the All GEN Analysis Set was as follows: GEN 323 (245.1) cells/µL (Section 15.1, Table 10.2).

Virologically Suppressed Subjects Who Switched Treatment

High rates of virologic suppression and high CD4 cell counts were maintained through the OL Extension Phase in subjects who switched to GEN from STB (referred to as the STB→GEN group in this report). In the STB→GEN group at Week 24 of the OL Extension Phase, 100% of subjects (57 of 57 subjects) had HIV-1 RNA < 50 copies/mL (M = E; Section 15.1, Table 9.2) and mean (SD) change from OL baseline in CD4 cell count was 9 (157.6) cells/µL (Section 15.1, Table 10.2).

Resistance Testing Results:

A total of 21 subjects (GEN 2.5%, 11 subjects; STB 2.3%, 10 subjects) met the protocol-defined criteria for resistance analyses through the end of the study and were included in the resistance analysis population (RAP), as presented in the table below. No new subjects met the protocol-defined criteria for resistance analyses after switching from STB to GEN. Resistance data were obtained for all subjects in the RAP except for 1 STB subject with both protease (PR)-reverse transcriptase (RT) and integrase (IN) assay failure (Appendix 16.2, Virology Listings 3 and 4).

In the GEN group, 3 subjects had HIV-1 with no emerging resistance and 8 subjects had HIV-1 with emerging resistance, as follows:

- 4 subjects whose HIV-1 had emerging M184V or M184I mixtures with wild-type alone in RT with no phenotypic resistance to FTC
- 1 subject whose HIV-1 had emerging K65R alone in RT with reduced susceptibility to both tenofovir (TFV) and FTC and IN assay failure

- 1 subject whose HIV-1 had emerging M184V in RT + INSTI-R (E92Q) with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging K65N + K70R in RT and N155H in IN with phenotypic resistance to TFV, FTC, and EVG
- 1 subject whose HIV-1 had emerging K65R + M184V in RT and N155H in IN with phenotypic resistance to FTC and EVG

In the STB group, 4 subjects had HIV-1 with no emerging resistance and 5 subjects had HIV-1 with emerging resistance, as follows:

- 1 subject whose HIV-1 had an emerging M184M/V mixture with wild-type alone in RT with no phenotypic resistance to FTC
- 1 subject whose HIV-1 had emerging M184V in RT + INSTI-R (E92E/Q + Q148R) with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging K65N + K70R in RT and N155H in IN with phenotypic resistance to TFV, FTC, and EVG
- 1 subject whose HIV-1 had emerging K65R + M184V in RT and E92Q in IN with uncharacterized phenotypic resistance to FTC and TFV (due to assay failure) and phenotypic resistance to EVG
- 1 subject whose HIV-1 showed the transient emergence of an L210L/W mixture with wild-type alone in RT with no phenotypic resistance to any of the study drugs

Resistance Category	Number of Subjects, n (%)	
	GEN (N = 435)	**STB (N = 432)**
RAP	11 (2.5%)	10 (2.3%)
Subjects with Data	11 (2.5%)	9 (2.1%)
With Emerging Resistance Mutations	8 (1.8%)	5 (1.2%)
No Emerging Resistance Mutations	3 (0.7%)	4 (0.9%)
Any Emerging NRTI-R	8 (1.8%)	5 (1.2%)
K65R/N	3 (0.7%)	2 (0.5%)
K70R	1 (0.2%)	1 (0.2%)
M184V/I	6 (1.4%)	3 (0.7%)
L210W	0	1 (0.2%)
Any Emerging Primary INSTI-R	3 (0.7%)	3 (0.7%)
E92Q/V	1 (0.2%)	2 (0.5%)
Q148R	0	1 (0.2%)
N155H/S	2 (0.5%)	1 (0.2%)

INSTI: integrase strand-transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; -R: resistant;
RAP: resistance analysis population
Source: Appendix 16.2, Virology Listings 1 to 4

Pharmacokinetics Results: No PK analyses were performed for this report. All PK data were presented in the Week 48 interim CSR.

Safety Results:

ART-Naive Subjects

Subjects in the Safety Analysis Set were exposed to double-blind GEN or STB for a median of 168.0 and 166.0 weeks, respectively (Section 15.1, Table 5.1). Median exposure to GEN in the All GEN Analysis Set was 172.0 weeks (Section 15.1, Table 5.2).

Adverse Events

Similar percentages of subjects in each group of the Safety Analysis Set had any AE (GEN 96.1%, 418 subjects; STB 96.1%, 415 subjects; Section 15.1, Table 11.1). The 3 most commonly reported AEs in the Double-Blind Phase were the same for each treatment group, as follows (Section 15.1, Table 12.1):

- GEN group — diarrhea (25.7%, 112 subjects), upper respiratory tract infection (21.4%, 93 subjects), and nausea (16.8%, 73 subjects)
- STB group — diarrhea (24.5%, 106 subjects), upper respiratory tract infection (22.0%, 95 subjects), and nausea (19.4%, 84 subjects)

The majority of the AEs reported in the Double-Blind Phase were Grade 1 or 2 (Section 15.1, Table 11.1). Similar percentages of subjects in each treatment group had any Grade 3 or 4 AEs (GEN 17.0%, 74 subjects; STB 15.0%, 65 subjects). The percentage of subjects that had any AE considered related to study drug by the investigator was lower in the GEN group than in the STB group (GEN 46.7%, 203 subjects; STB 53.2%, 230 subjects). The majority of AEs considered related to study drug by the investigator were Grade 1. The incidence of Grade 3 or 4 AEs considered related to study drug was low in both treatment groups (GEN 2.5%, 11 subjects; STB 1.2%, 5 subjects).

Four treatment-emergent deaths were reported during the Double-Blind Phase, 2 subjects in each treatment group. One subject in the GEN group died as a result of embolic stroke in the setting of atrial fibrillation that transformed into hemorrhagic stroke. The other subject in the GEN group died as a result of suicide by gunshot. One subject in the STB group died as a result of cardiac arrest in the setting of postoperative, vagally mediated bradycardia and asystole. The other subject in the STB group died of unknown causes. One additional death was reported in the STB group, which was not treatment emergent. None of the deaths were considered related to study drug by the investigator.

Serious adverse events (SAEs) were reported for similar percentages of subjects in each treatment group during the Double-Blind Phase (GEN 16.8%, 73 subjects; STB 15.0%, 65 subjects). The incidence of SAEs considered related to study drug by the investigator was low in both treatment groups (GEN 1.1%, 5 subjects; STB 0.5%, 2 subjects).

The incidence of AEs that led to discontinuation of study drug during the Double-Blind Phase was lower in the GEN group than in the STB group, as follows: GEN 1.4%, 6 subjects; STB 4.6%, 20 subjects. No subject in the GEN group discontinued study drug due to a study drug-related bone or renal and urinary disorder or associated investigation AE; in the STB group, 13 subjects discontinued study drug due to study drug-related bone or renal and urinary disorder

or associated investigation AEs (Appendix 16.2, Listing 20). Adverse events leading to discontinuation of study drug that were considered related to study drug by the investigator were reported for 3 subjects in the GEN group and 16 subjects in the STB group.

Six confirmed pregnancies were reported during the study, 3 in each treatment group. Two resulted in deliveries of healthy baby girls with no complications, 1 was terminated with omphalocele and trisomy of chromosome 18, 1 was terminated with no evidence of structural defect, 1 resulted in miscarriage, and 1 was lost to follow-up.

The AE profile of GEN through the OL Extension Phase was mostly unchanged from that reported for the Double-Blind Phase, with minimal or no change in overall AE incidence or in the incidence of the 3 most common AEs (diarrhea, upper respiratory tract infection, and nausea), Grade 3 or 4 AEs, study drug-related AEs, or SAEs (Section 15.1, Table 11.2). No additional deaths or AEs leading to discontinuation of study drug were reported in the OL Extension Phase.

Bone Safety

Incidence of discontinuations due to bone AEs and the effects on BMD at the hip or spine continue to favor treatment with GEN over treatment with STB.

In the GEN group, no subjects discontinued study drug due to a bone AE (Appendix 16.2, Listing 20). Five subjects in the STB group had bone AEs that resulted in discontinuation of study drug (osteopenia [1 subject], bone loss [1 subject], osteoporosis [1 subject], and bone density decreased [2 subjects]).

Mean percentage decreases from baseline in BMD at the hip or spine were smaller in the GEN group than in the STB group. For both the hip and spine, the difference between treatment groups in percentage change from baseline was statistically significant at all measured time points from Weeks 24 to 168 ($p < 0.001$).

Mean (SD) percentage decreases from baseline at Week 168 in BMD were as follows (Section 15.1, Tables 27.1.1 and 27.2.1):

- **Hip:** GEN 0.428% (5.0089%); STB 3.876% (4.1679%)
- **Spine:** GEN 0.851% (4.8110%); STB 3.313% (5.5862%)

The bone safety profile of GEN through the OL Extension Phase was mostly unchanged from that reported for the Double-Blind Phase, with no subjects discontinuing study drug due to a bone AE (Appendix 16.2, Listing 20) and similar BMD findings through the end of the study (Section 15.1, Tables 27.1.2 and 27.2.2).

Renal Safety

Incidence of discontinuations of study drug due to renal and urinary disorder or associated investigation AEs, the effects on serum creatinine and eGFR, and measures of proteinuria and proximal tubular proteinuria continue to favor treatment with GEN over treatment with STB. In the GEN group, there were no reports of proximal renal tubulopathy (including Fanconi syndrome), compared with 3 events considered tubulopathy or Fanconi syndrome in the STB group (Appendix 16.2, Listing 17).

No subject in the GEN group discontinued study drug due to a renal and urinary disorder or associated investigation AE, compared with 8 subjects in the STB group who discontinued study drug due to renal and urinary disorder or associated investigation AEs (Appendix 16.2, Listing 20). Renal and urinary disorder or associated investigation AEs that resulted in discontinuation of study drug were as follows: renal tubular disorder (3 subjects), nephropathy (1 subject), renal failure (1 subject), decreased GFR (1 subject), increased blood creatinine and decreased GFR (1 subject), and proteinuria (1 subject). All events were nonserious.

Renal SAEs were reported in 2 subjects in the GEN group (nephrotic syndrome and postinfectious glomerulonephritis [1 subject each]) and 1 subject in the STB group (acute kidney injury); no renal SAE was considered related to study drug by the investigator, and each resolved without interruption or discontinuation of study drug (Appendix 16.2, Listing 19.1).

Increases from baseline in mean values for serum creatinine were smaller in the GEN group than in the STB group (Section 15.1, Table 28.1). Increases were observed by Week 2 in both treatment groups, and remained evident through Week 168. Mean (SD) changes from baseline at Week 168 were as follows: GEN 0.03 (0.118) mg/dL, STB 0.09 (0.142) mg/dL. The difference in changes from baseline between the treatment groups was statistically significant at all time points from Weeks 2 to 168, except Week 108.

Decreases from baseline in median $eGFR_{CG}$ values were smaller in the GEN group than in the STB group (Section 15.1, Table 29.1). Decreases were observed by Week 2 in both treatment groups that remained evident through Week 168. Median (Q1, Q3) changes from baseline at Week 168 were as follows: GEN −1.0 (−12.5, 9.8) mL/min, STB −9.6 (−20.0, 2.8) mL/min. The difference between treatment groups was statistically significant at all time points from Weeks 2 to 168 ($p < 0.001$ at Week 168).

For UPCR, there were statistically significant differences between treatment groups at all time points from Weeks 2 to 168 ($p = 0.002$ at Week 168; Section 15.1, Table 30.4.1). Median (Q1, Q3) percentage changes from baseline at Week 168 were as follows: GEN −18.3% (−48.5%, 32.3%), STB −2.8% (−35.6%, 64.3%). Urine creatinine was similar between treatment groups at each measured time point through Week 168.

There were statistically significant differences in changes from baseline between treatment groups in specific markers of proximal tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio) at all time points through Week 168 ($p < 0.001$). Median (Q1, Q3) percentage changes from baseline at Week 168 were as follows: urine RBP to creatinine ratio (Section 15.1, Table 30.2.1) GEN 54.4% (13.2%, 124.3%), STB 147.2% (53.4%, 413.8%); urine beta-2-microglobulin to creatinine ratio (Section 15.1, Table 30.3.1) GEN −23.0% (−62.4%, 21.7%), STB: 50.0% (−22.6%, 498.2%).

The renal safety profile of GEN through the OL Extension Phase was mostly unchanged from that reported in the Double-Blind Phase, with no subjects discontinuing study drug due to renal and urinary disorder or associated investigation AEs during the OL Extension Phase (Appendix 16.2, Listing 20), no new renal SAEs reported (Section 15.1, Table 18.2), and similar renal laboratory parameter findings through the end of the study (Section 15.1, Tables 28.2, 29.2, 30.4.2, 30.2.2, and 30.3.2).

Laboratory Abnormalities

There were no clinically relevant changes from baseline within groups, or differences between the treatment groups in median values for hematology or clinical chemistry parameters, and all median values were within normal ranges (Section 15.1, Tables 24.1.1, 24.2.1, 24.3.1, 24.4.1, 24.5.1, 24.6.1, 24.7.1, 24.8.1, 24.9.1, 24.10.1, 24.11.1, 24.12.1, 24.13.1, 25.1.1, 25.2.1, 25.3.1, 25.4.1, 25.5.1, 25.6.1, 25.7.1, 25.8.1, 25.9.1, 25.10.1, 25.11.1, 25.12.1, 25.13.1, 25.14.1, 25.15.1, 25.16.1, 25.17.1, 25.18.1, 25.19.1, 25.20.1, 25.21.1, 25.22.1, and 25.23.1). The majority of subjects had at least 1 laboratory abnormality during the Double-Blind Phase (GEN 97.9%, 425 subjects; STB 97.4%, 420 subjects; Section 15.1, Table 21.1). The majority of reported abnormalities were Grade 1 or 2. Grade 3 or 4 laboratory abnormalities were reported for 34.6% of subjects in the GEN group and 30.9% of subjects in the STB group, the incidence of all Grade 3 or 4 laboratory abnormalities was similar between the 2 treatment groups (Section 15.1, Table 22.1).

The laboratory parameter safety profile of GEN through the OL Extension Phase was mostly unchanged from that reported in the Double-Blind Phase, with minimal or no change in the incidence of any laboratory abnormality or Grade 3 or 4 laboratory abnormalities (Section 15.1, Tables 21.2 and 22.2).

Metabolic Laboratory Parameters

Increases from baseline were observed in both treatment groups for the fasting lipid parameters (total cholesterol, direct low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides) and glucose at Week 168. The majority of the increases for the fasting lipid parameters were seen in the first 24 weeks; values then remained stable through Week 168. Median (Q1, Q3) increases from baseline in fasting lipid parameters were greater in the GEN group than in the STB group at Week 168, as follows: total cholesterol (Section 15.1, Table 26.1.1) GEN 33 (12, 54) mg/dL; STB 15 (−3, 34) mg/dL ($p < 0.001$); direct LDL (Section 15.1, Table 26.2.1) GEN 20 (6, 40) mg/dL; STB 10 (−5, 26) mg/dL ($p < 0.001$); HDL (Section 15.1, Table 26.3.1) GEN 7 (1, 15) mg/dL; STB 2 (−4, 9) mg/dL ($p < 0.001$). For total cholesterol to HDL ratio, fasting triglycerides, and fasting glucose, there were no differences between treatment groups in changes from baseline at Week 168. Median (Q1, Q3) changes from baseline at Week 168 were as follows: total cholesterol to HDL ratio (Section 15.1, Table 26.4.1) GEN 0.1 (−0.4, 0.6); STB 0.1 (−0.4, 0.7) ($p = 0.61$); fasting triglycerides (Section 15.1, Table 26.5.1) GEN 19 (−14, 61) mg/dL; STB 17 (−8, 52) mg/dL ($p = 0.91$); fasting glucose (Section 15.1, Table 26.6.1) GEN 2 (−3, 9) mg/dL; STB 2 (−6, 11) mg/dL ($p = 0.70$).

In general, graded laboratory abnormalities related to lipid parameters were more common in the GEN group than in the STB group. The majority of laboratory abnormalities related to lipid parameters were Grade 1 or 2; Grade 3 or 4 abnormalities were infrequent, and reported for similar percentages of subjects in each treatment group.

The metabolic laboratory parameter safety profile of GEN through the OL Extension Phase was mostly unchanged from that reported in the Double-Blind Phase (Section 15.1, Tables 26.1.2, 26.2.2, 26.3.2, 26.4.2, 26.5.2, and 26.6.2).

Virologically Suppressed Subjects Who Switched Treatment

Among the 94 subjects who switch to GEN from STB in the OL Extension Phase (referred to as the STB→GEN group in this report), median exposure to OL GEN was 23.3 weeks (Section 15.1, Table 5.2).

Adverse Events

Among the subjects in the STB→GEN group, 28.7% of subjects (27 of 94 subjects) had any AE (Section 15.1, Table 11.2). The most commonly reported AEs for this group in the OL Extension Phase (those reported in more than 1 subject) were as follows (Section 15.1, Table 12.2):

- STB→GEN group — attention deficit/hyperactivity disorder, gonorrhea, syphilis, upper respiratory tract infection (each 2.1%, 2 subjects)

In the STB→GEN group during the OL Extension Phase, all AEs reported were Grade 1 or 2, and none were considered related to study drug by the investigator (Section 15.1, Table 11.2).

Serious AEs were reported for 1.1% of subjects (1 subject) in the STB→GEN group during the OL Extension Phase; the events were not considered related to study drug by the investigator (Section 15.1, Table 11.2).

No additional deaths or AEs leading to discontinuation of study drug were reported in the OL Extension Phase.

Bone Safety

No subjects discontinued study drug due to a bone AE during the OL Extension Phase (Appendix 16.2, Listing 20).

Small increases from OL baseline in BMD at the hip or spine were observed in the STB→GEN group. Mean (SD) percentage increases from OL baseline in BMD at Week 24 of the OL Extension Phase were as follows (Section 15.1, Tables 27.1.2 and 27.2.2):

- **Hip:** STB→GEN 0.492% (1.7623%)
- **Spine:** STB→GEN 1.133% (1.9332%)

Renal Safety

No subjects discontinued study drug due to renal and urinary disorder or associated investigation AEs during the OL Extension Phase (Appendix 16.2, Listing 20), and no new renal SAEs were reported (Section 15.1, Table 18.2).

Small decreases from OL baseline in mean serum creatinine were observed in the STB→GEN group. Mean (SD) change from OL baseline in serum creatinine at Week 24 of the OL Extension Phase was −0.01 (0.119) mg/dL (Section 15.1, Table 28.2).

Small increases from OL baseline in median $eGFR_{CG}$ were observed in the STB→GEN group. Median (Q1, Q3) change from OL baseline in $eGFR_{CG}$ at Week 24 of the OL Extension Phase was 2.0 (−5.4, 8.7) mL/min (Section 15.1, Table 29.2).

Decreases from OL baseline in median UPCR were observed in the STB→GEN group; median (Q1, Q3) percentage change from OL baseline at Week 24 of the OL Extension Phase was −17.6% (−36.5%, 103.6%; Section 15.1, Table 30.4.2).

Decreases from OL baseline in specific markers of proximal tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio) were observed in the STB→GEN group. Median (Q1, Q3) percentage changes from OL baseline at Week 24 of the OL Extension Phase were as follows: urine RBP to creatinine ratio (Section 15.1, Table 30.2.2) −21.9% (−39.0%, 36.5%); urine beta-2-microglobulin to creatinine ratio (Section 15.1, Table 30.3.2) −36.8% (−69.5%, 23.5%).

Laboratory Abnormalities

There were no clinically relevant changes from OL baseline in median values for hematology or clinical chemistry parameters for the STB→GEN group, and all median values were within normal ranges (Section 15.1, Tables 24.1.2, 24.2.2, 24.3.2, 24.4.2, 24.5.2, 24.6.2, 24.7.2, 24.8.2, 24.9.2, 24.10.2, 24.11.2, 24.12.2, 24.13.2, 25.1.2, 25.2.2, 25.3.2, 25.4.2, 25.5.2, 25.6.2, 25.7.2, 25.8.2, 25.9.2, 25.10.2, 25.11.2, 25.12.2, 25.13.2, 25.14.2, 25.15.2, 25.16.2, 25.17.2, 25.18.2, 25.19.2, 25.20.2, 25.21.2, 25.22.2, and 25.23.2). Laboratory abnormalities were reported for 64.4% of subjects (58 of 90 subjects) in the STB→GEN group during the OL Extension Phase (Section 15.1, Table 21.2). The majority of reported abnormalities were Grade 1 or 2. Grade 3 or 4 laboratory abnormalities were reported for 10.0% of subjects in the STB→GEN group (Section 15.1, Table 22.2).

Metabolic Laboratory Parameters

Increases from OL baseline were observed in the STB→GEN group for the fasting lipid parameters (total cholesterol, direct LDL, HDL, and triglycerides). Median (Q1, Q3) changes from OL baseline in fasting lipid parameters and fasting glucose in the STB→GEN group at Week 24 of the OL Extension Phase were as follows: total cholesterol (Section 15.1, Table 26.1.2) 27 (2, 52) mg/dL; direct LDL (Section 15.1, Table 26.2.2) 22 (−4, 39) mg/dL; HDL (Section 15.1, Table 26.3.2) 2 (−5, 7) mg/dL; total cholesterol to HDL ratio (Section 15.1, Table 26.4.2) 0.4 (0.0, 1.0); triglycerides (Section 15.1, Table 26.5.2) 23 (−22, 82) mg/dL; and glucose (Section 15.1, Table 26.6.2) 1 (−6, 7) mg/dL.

CONCLUSIONS: The conclusions from this final analysis are as follows:

- High rates of virologic suppression were achieved and maintained through the Double-Blind Phase in HIV-1 infected, ART naive adults who received GEN or STB once daily. The percentages of subjects with HIV-1 RNA < 50 copies/mL were as follows: M = F at Week 156 GEN 85.3%; STB 84.7%; difference in percentages: 0.8%, 95% CI: −4.0% to 5.6%; M = E at Week 168 GEN 98.6%; STB 98.2%; difference in percentages: 0.5%, 95% CI: −2.0% to 2.9%. Both groups had increases from baseline in mean CD4 cell counts (Week 168: GEN 342 cells/μL; STB 349 cells/μL).
- GEN was better tolerated than STB with lower rates of AEs considered related to study drug and AEs leading to discontinuation of study drug.
- GEN was associated with an improved bone and renal safety profile compared with STB, as evidenced by the following:
  - Less decline in hip and spine BMD in subjects who received GEN relative to those who received STB
  - No cases of proximal renal tubulopathy (including Fanconi syndrome) or and no renal and urinary disorder or associated investigation AEs leading to discontinuation of study drug in the GEN group compared with 8 renal and urinary disorder or associated investigation AEs leading to discontinuation of study drug, including 3 cases of renal tubular disorder, in the STB group
  - Less increase in serum creatinine and less reduction in $eGFR_{CG}$ in subjects who received GEN relative to those who received STB

  - — Decreases in proteinuria by quantitative assessment (UPCR) in subjects who received GEN compared with increases in subjects who received STB
  - — Decreases (urine beta-2-microglobulin to creatinine ratio) or less increase (urine RBP to creatinine ratio) in renal tubular proteinuria in those who received GEN compared with increases in those who received STB
- Increases from baseline in fasting lipid parameters were higher in the GEN group than the STB group. The majority of these increases were seen in the first 24 weeks; values then remained stable through Week 168.
- In HIV-infected, virologically suppressed subjects who switched to GEN from STB, GEN was well tolerated with low rates of SAEs and no AE-related drug discontinuation.
- HIV-infected subjects who switched to GEN from STB showed signs of improved bone and renal safety parameters through 24 weeks of treatment after switching, consistent with previous results in studies of virologically suppressed subjects switching to GEN from TDF-based regimens.