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:	HIV-1 infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-292-0111
Phase of Development:	Phase 3
IND No.:	111007
EudraCT No.:	2013-000102-37
ClinicalTrials.gov Identifier:	NCT01797445
Study Start Date:	12 March 2013 (First Subject Screened)
Study End Date:	19 September 2014 (Last Subject Last Observation for the Primary Endpoint) 03 October 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: David Wohl, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Christoph Carter, MD, PhD Telephone: PPD Fax: PPD
Report Date:	06 February 2019
Previous Report Date(s):	21 September 2016 (Week 144 Clinical Study Report) 02 October 2015 (Week 96 Clinical Study Report) 13 October 2014 (Week 48 Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-292-0111

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 is a multicenter study.

Study Centers: Subjects were enrolled in a total of 121 study centers: 82 in the United States (US), 10 in the United Kingdom, 9 in France, 5 in Canada, 4 in Italy, 4 in Portugal, 2 in Mexico, 2 in Netherlands, 2 in Sweden, and 1 in Dominican Republic.

Publications:

Margot N, Cox S, Das M, McCallister S, Miller MD, Callebaut C. Rare emergence of drug resistance in HIV-1 treatment-naive patients receiving elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide for 144 weeks. J Clin Virol 2018;103:37-42.

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-naive 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:

12 March 2013 (First Subject Screened)
19 September 2014 (Last Subject Last Observation for the Primary Endpoint)
03 October 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives: Study GS-US-292-0111 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 EVG/COBI/FTC/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 Weeks 48 and 96 interim clinical study reports (CSRs) and are not addressed further in this report. The remaining secondary objectives were addressed in the Week 144 interim 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, active-controlled, multicenter study that evaluated the efficacy and safety of a regimen that contained 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 drugs 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	435	437	872
Subjects in Safety Analysis Set	431 (99.1%)	435 (99.5%)	866 (99.3%)
Subjects in FAS	431 (99.1%)	435 (99.5%)	866 (99.3%)
Subjects in Hip DXA Analysis Set	412 (94.7%)	424 (97.0%)	836 (95.9%)
Subjects in Spine DXA Analysis Set	418 (96.1%)	425 (97.3%)	843 (96.7%)

DXA = dual-energy x-ray absorptiometry; FAS = Full Analysis Set
The denominator for percentages was 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	431	119
Subjects in All GEN Hip DXA Analysis Set	412 (95.6%)	119 (100.0%)
Subjects in All GEN Spine DXA Analysis Set	418 (97.0%)	119 (100.0%)

DXA = dual-energy x-ray absorptiometry
The denominator for percentages was 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 TDF, and had an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 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: CP1205B1, CP1208B1, CP1209B1, CP1305B1, CP1307B1, CP1311B1, CP1313B1, CP1314B1, CP1402B1, CP1401B1, CP1405B1, CP1501B1, CP1504B1, CP1604B1, and CP1306B1

Placebo-to-match STB: BK1205B1R, BK1206B1R, BK1302B1, 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: BK1203B1, BK1204B1, BK1303B1, BK1304B1, 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 achieved 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 Weeks 48 and 96 interim CSRs. Results for secondary efficacy endpoints at Weeks 48, 96, and 144 were described in the Weeks 48, 96, and 144 interim CSRs, respectively.

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

Other: Results for the EQ-5D-3L health-outcomes questionnaire were described in the Weeks 48 and 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 Weeks 48, 96, and 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 21.0. 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 and Demographics: A total of 866 subjects were randomized and received at least 1 dose of study drug in the Double-Blind Phase (GEN 431 subjects; STB 435 subjects; Section 15.1, Table 1). Of the 866 randomized and treated subjects, 676 subjects (GEN 79.8%, 344 subjects; STB 76.3%, 332 subjects) completed study drug in the Double-Blind Phase, and 260 subjects (GEN 32.7%, 141 subjects; STB 27.4%, 119 subjects) entered the OL Extension Phase and received at least 1 dose of OL GEN.

A total of 190 subjects (GEN 20.2%, 87 subjects; STB 23.7%, 103 subjects) prematurely discontinued study drug in the Double-Blind Phase. The most common reasons for premature discontinuation of study drug during the Double-Blind Phase were lost to follow-up (GEN 7.2%, 31 subjects; STB 5.7%, 25 subjects), withdrawal of consent (GEN 3.9%, 17 subjects; STB 7.1%, 31 subjects), and investigator's discretion (GEN 3.9%, 17 subjects; STB 4.4%, 19 subjects). A total of 10 subjects (GEN 5.7%, 8 subjects; subjects who switched to GEN from STB [referred to as STB→GEN in this report] 1.7%, 2 subjects) discontinued study drug in the OL Extension Phase. The reasons for premature discontinuation of study drug during the OL Extension Phase were lost to follow-up (GEN 3.5%, 5 subjects; STB→GEN 1.7%, 2 subjects), investigator's discretion (GEN 1.4%, 2 subjects; STB→GEN 0 subjects), and protocol violation (GEN 0.7%, 1 subject; STB→GEN 0 subjects).

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 (84.6% overall). The median ages were as follows: GEN 33 years (range: 18 to 66); STB 34 years (range: 18 to 71; p = 0.049). The most common races were white (55.2%), black (30.1%), and other (10.5%). Most subjects were not Hispanic or Latino (76.2%). Overall, the median (first quartile [Q1], third quartile [Q3]) baseline body mass index was 24.7 (22.1, 28.2) 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 4.55 (4.12, 4.94) log_{10} copies/mL. At baseline, 77.9% of subjects had HIV-1 RNA ≤ 100,000 copies/mL, 17.3% of subjects had HIV-1 RNA > 100,000 to ≤ 400,000 copies/mL, and 4.7% of subjects had HIV-1 RNA > 400,000 copies/mL. Overall, the median (Q1, Q3) baseline CD4 count was 406 (284, 536) cells/μL. At baseline, 3.4% of subjects had a CD4 cell count < 50 cells/μL, and 10.3% of subjects had a CD4 cell count ≥ 50 to < 200 cells/μL. The most common HIV risk factor category was homosexual sex (74.9% of subjects). Few subjects (5.7%) had symptomatic HIV-1 infection, and 4.8% of subjects were diagnosed with AIDS.

At baseline, the median (Q1, Q3) $eGFR_{CG}$ value was similar in the GEN group (115.9 [98.4, 135.6] mL/min) compared with the STB group (114.7 [99.6, 133.4] mL/min).

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 Weeks 48, 96, and 144 as defined by the US FDA-defined snapshot algorithm were described in the Weeks 48, 96, and 144 interim CSRs, respectively.

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 = E at Week 156 (Section 15.1, Table 9.1): GEN 96.9% (339 of 350 subjects); STB 97.2% (344 of 354 subjects); difference in percentages: −0.5% (95% CI: −3.2%, 2.3%)
- M = E at Week 168 (Section 15.1, Table 9.1): GEN 97.3% (217 of 223 subjects); STB 96.2% (201 of 209 subjects); difference in percentages: 1.4% (95% CI: −2.4%, 5.3%)
- M = E at Week 192 (Section 15.1, Table 9.2): GEN 96.5% (82 of 85 subjects)
- M = E at Week 240 (Section 15.1, Table 9.2): GEN 100.0% (24 of 24 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 332 (228.0) cells/μL; STB 310 (219.5) cells/μL; difference in least-squares mean (LSM): 26 cells/μL (95% CI: −20, 72). In the GEN group, the mean (SD) increases from baseline in CD4 cell counts using the All GEN Analysis Set were as follows (Section 15.1, Table 10.2):
Week 192: 323 (192.9) cells/μL; Week 240: 376 (231.6) cells/μL.

Virologically Suppressed Subjects Who Switched Treatment

High rates of virologic suppression and high CD4 cell counts were maintained through the OL Extension Phase in the STB→GEN group. Using the M = E method, percentages of subjects with HIV-1 RNA < 50 copies/mL in the STB→GEN group were as follows (Section 15.1, Table 9.2): Week 24: 98.8% (79 of 80 subjects); Week 48: 100.0% (26 of 26 subjects); Week 96: 100.0% (13 of 13 subjects). The mean (SD) increases from OL baseline in CD4 cell counts were as follows (Section 15.1, Table 10.2): Week 24: 3 (129.0) cells/μL; Week 48: 79 (241.5) cells/μL; Week 96: 167 (281.5) cells/μL.

Resistance Testing Results:

Through the end of the study, a total of 43 subjects (GEN 5.1%, 22 subjects; STB 4.8%, 21 subjects) met the protocol-defined criteria for resistance analyses and were included in the resistance analysis population (RAP), as presented in the table below. One new subject met the protocol-defined criteria for resistance analyses after switching from STB to GEN, with no HIV-1 resistance emerging. Resistance data were obtained for all subjects in the RAP except for 1 GEN and 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, 16 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 emerging M184V in RT and E92Q in IN with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging M184V in RT and E92Q in IN with phenotypic resistance to FTC and uncharacterized phenotypic resistance to EVG (due to assay failure)
- 1 subject whose HIV-1 had emerging M184I in RT and E92Q in IN with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging M184V in RT and T66A/I/T/V + Q148Q/R in IN with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging M184V in RT and T66A in IN with phenotypic resistance to both FTC and EVG

In the STB group, 13 subjects had HIV-1 with no emerging resistance, and 7 subjects had HIV-1 with emerging resistance, as follows:

- 1 subject whose HIV-1 had emerging M184V only in RT with phenotypic resistance to FTC
- 1 subject whose HIV-1 had emerging M184M/V only in RT with no phenotypic resistance to FTC
- 1 subject whose HIV-1 had emerging M184V in RT and E92V in IN with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging A62A/V + K65R + M184V in RT and E92Q in IN with phenotypic resistance to tenofovir, FTC, and EVG
- 1 subject whose HIV-1 had emerging K65R + M184V in RT and Q148R in IN with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging M184V in RT and N155H in IN with phenotypic resistance to both FTC and EVG
- 1 subject whose HIV-1 had emerging N155N/S alone in IN with uncharacterized phenotypic resistance to EVG and no PR-RT genotypic and phenotypic data (due to assay failure)

Resistance Category	Number of Subjects, n (%)	
	GEN (N = 431)	STB (N = 435)
RAP	22 (5.1%)	21 (4.8%)
Subjects with Data	21 (4.9%)	20 (4.6%)
With Emerging Resistance Mutations	5 (1.2%)	7 (1.6%)
No Emerging Resistance Mutations	16 (3.7%)	13 (3.0%)
Any Emerging NRTI-R	5 (1.2%)	6 (1.4%)
A62V	0	1 (0.2%)
K65N/R	0	2 (0.5%)
M184I/V	5 (1.2%)	6 (1.4%)
Any Emerging Primary INSTI-R	5 (1.2%)	5 (1.1%)
T66A/I/K	2 (0.5%)	0
E92G/Q/V	3 (0.7%)	2 (0.5%)
Q148H/K/R	1 (0.2%)	1 (0.2%)
N155H/S	0	2 (0.5%)

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 160.0 and 158.1 weeks, respectively (Section 15.1, Table 5.1). Median exposure to GEN in the All GEN Analysis Set was 167.6 weeks (Section 15.1, Table 5.2).

Adverse Events

Similar percentages of subjects in each treatment group of the Safety Analysis Set had any AE (GEN 93.0%, 401 subjects; STB 96.3%, 419 subjects; Section 15.1, Table 11.1). The 3 most commonly reported AEs in the Double-Blind Phase were as follows (Section 15.1, Table 12.1):

- GEN group — diarrhea or headache (each 23.0%, 99 subjects), and upper respiratory tract infection (20.2%, 87 subjects)
- STB group — diarrhea (26.2%, 114 subjects), nausea (19.8%, 86 subjects), and upper respiratory tract infection (18.9%, 82 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 AE (GEN 16.5%, 71 subjects; STB 17.9%, 78 subjects). The percentage of subjects that had any AE considered related to study drug by the investigator was lower in the GEN group compared with

the STB group (GEN 42.0%, 181 subjects; STB 46.4%, 202 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 numerically lower in the GEN group compared with the STB group (GEN 0.9%, 4 subjects; STB 2.5%, 11 subjects).

Four treatment-emergent deaths were reported in each treatment group during the Double-Blind Phase (Section 15.1, Table 11.1). In the GEN group, the causes of death were as follows: completed suicide (2 subjects), alcohol poisoning (1 subject), and cerebrovascular accident (1 subject). In the STB group, the causes of death were as follows: acute myocardial infarction, an unknown cause, cardiac arrest, and overdose (1 subject each). One additional death was reported in the GEN group, which was not treatment emergent; this subject died of myocardial infarction, which occurred > 30 days after the last dose of study drug. None of the deaths were considered related to study drug by the investigator (Appendix 16.2, Listings 19.1 and 22).

Similar percentages of subjects in each treatment group had any serious adverse event (SAE) during the Double-Blind Phase (GEN 12.5%, 54 subjects; STB 15.6%, 68 subjects). The incidence of SAEs considered related to study drug by the investigator was low in both treatment groups (GEN 0 subjects; STB 0.9%, 4 subjects; Section 15.1, Table 11.1).

The incidence of AEs that led to discontinuation of study drug during the Double-Blind Phase was lower in the GEN group compared with the STB group (GEN 1.4%, 6 subjects; STB 2.3%, 10 subjects; Section 15.1, Table 11.1). In the GEN group, no subject discontinued study drug due to a study drug-related bone or renal and urinary disorder or associated investigation AE. In the STB group, 4 subjects discontinued study drug due to study drug-related bone or renal and urinary disorder or associated investigation AEs. Adverse events leading to discontinuation of study drug that were considered related to study drug by the investigator were reported for 4 subjects in the GEN group and 9 subjects in the STB group. Since the Week 144 interim CSR, no new study-drug related AEs leading to discontinuation of study drug were reported in the GEN group during the Double-Blind Phase. In the STB group, 1 additional study drug-related AE of hypertriglyceridemia that led to discontinuation of study drug was reported during the Double-Blind Phase (Appendix 16.2, Listing 20).

Eleven confirmed pregnancies were reported for 7 subjects during the study, all in the STB group (Appendix 16.2, Listing 33). Four pregnancies resulted in the deliveries of healthy babies without complications (1 baby had a 1.2 mm ventricular septal defect that resolved within 2 days, as confirmed by a follow-up echocardiogram), 2 pregnancies resulted in spontaneous abortions, 1 pregnancy resulted in the delivery of a preterm baby with cryptorchidism, 1 baby experienced severe intrauterine growth restriction, 1 baby experienced a broken leg (with possible cause reported as delivery), and 1 pregnancy had an unknown status. One pregnancy resulted in the delivery of a healthy baby with complications of uterine rupture, which the investigator noted to be normal spontaneous rupture of membrane (water breaking), and a decreased platelet count (the subject received a transfusion while in the hospital).

The AE 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 overall AE incidence or in the incidences of the 3 most common AEs (headache, diarrhea, and upper respiratory tract infection), Grade 3 or 4 AEs, study drug-related AEs, or SAEs (Section 15.1, Tables 11.2 and 12.2). 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. One subject in the STB group discontinued study drug due to a nonserious AE of bone density decreased, which was considered related to study drug by the investigator. This subject also discontinued study drug due to an AE of blood creatinine increase (Appendix 16.2, Listing 20).

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

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 1.217% (4.3351%); STB 3.352% (4.5958%)
- **Spine:** GEN 1.574% (4.9895%); STB 3.456% (5.1197%)

The bone 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 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 1 event 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 4 subjects in the STB group who discontinued study drug due to renal and urinary disorder or associated investigation AEs (Appendix 16.2, Listing 20). In the STB group, renal and urinary disorder or associated investigation AEs that resulted in discontinuation of study drug were as follows: renal failure (1 subject), acquired Fanconi syndrome (indicative of proximal renal tubulopathy) and glycosuria (1 subject), blood creatinine increased (1 subject), and bladder spasm (1 subject). The subject who reported the AE of blood creatinine increased also reported an AE of bone density decreased. The event of bladder spasm was not considered an intrinsic kidney disorder. All events were nonserious.

Renal SAEs were reported for 1 subject in the GEN group (ureterolithiasis) and 2 subjects in the STB group (ureterolithiasis and renal hematoma [1 subject each]). 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 compared with 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 0.05 (0.127) mg/dL; STB 0.07 (0.150) mg/dL. The differences in changes from baseline between treatment groups were statistically significant at all time points from Weeks 2 through 168 ($p = 0.040$ at Week 168).

Decreases from baseline in median $eGFR_{CG}$ values were smaller in the GEN group compared with the STB group (Section 15.1, Table 29.1). Decreases were observed by Week 2 in both treatment groups and remained evident through Week 168. Median (Q1, Q3) changes from baseline at Week 168 were as follows: GEN −1.3 (−12.1, 7.9) mL/min; STB −7.9 (−19.4, 2.9) mL/min. The differences in changes from baseline between treatment groups were statistically significant at all time points from Weeks 2 through 168 ($p < 0.001$ at each time point).

A decrease from baseline in median UPCR was observed in the GEN group at Week 2 which persisted through Week 168, whereas an increase from baseline in median UPCR was observed in the STB group at Week 2 which persisted through Week 144 (Section 15.1, Table 30.4.1). Median (Q1, Q3) percentage changes from baseline at Week 168 were as follows: GEN −23.4% (−55.4%, 27.3%); STB −15.5% (−46.4%, 31.3%). For UPCR, the differences in percentage changes from baseline between treatment groups were statistically significant at all time points from Weeks 2 through 156 ($p < 0.001$ at each time point). The changes from baseline in urine creatinine were similar between treatment groups at each measured time point through Week 168 (Section 15.1, Table 30.1.1).

There were statistically significant differences in percentage 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 ($p = 0.005$ for urine RBP to creatinine ratio and $p = 0.003$ for urine beta-2-microglobulin to creatinine ratio at Week 168; Section 15.1, Tables 30.2.1 and 30.3.1). Median (Q1, Q3) percentage changes from baseline at Week 168 for urine RBP to creatinine ratio were as follows: GEN 54.4% (18.6%, 112.7%); STB 182.3% (38.6%, 371.6%). Median (Q1, Q3) percentage changes from baseline at Week 168 for urine beta-2-microglobulin to creatinine ratio were as follows: GEN −17.6% (−49.6%, 27.9%); STB: 27.0% (−20.0%, 487.5%).

The renal safety profile of GEN through the OL Extension Phase was mostly unchanged from that reported in the Double-Blind Phase. One subject reported a Grade 1 AE of glomerular filtration rate decreased which was considered related to study drug by the investigator; this event was considered nonserious and resolved without interruption or discontinuation of study drug (Appendix 16.2, Listing 17). During the OL Extension Phase, no subjects prematurely discontinued study drug due to renal and urinary disorder or associated investigation AEs (Appendix 16.2, Listing 20), no new renal SAEs were reported (Section 15.1, Table 18.2), and similar renal laboratory parameter findings were observed through the end of the study (Section 15.1, Tables 28.2, 29.2, 30.2.2, 30.3.2, and 30.4.2).

Laboratory Abnormalities

There were no clinically relevant changes from baseline within groups or differences between treatment groups in median values for hematology or clinical chemistry parameters. Generally, the 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 98.6%, 422 of 428 subjects; STB 96.8%, 420 of 434 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 as follows: GEN 34.1%, 146 subjects; STB 33.4%, 145 subjects. The incidences of all Grade 3 or 4 laboratory abnormalities were similar between the 2 treatment groups, with the exception of Grade 3 or 4 amylase abnormalities (GEN 1.6%, 7 of 428 subjects; STB 6.2%, 27 of 434 subjects) and Grade 3 or 4 lipase abnormalities (GEN 2.9%, 2 of 68 subjects; STB 9.3%, 8 of 86 subjects; 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 compared with the STB group at Week 168, as follows: total cholesterol: GEN 33 (13, 59) mg/dL, STB 20 (3, 35) mg/dL ($p < 0.001$; Section 15.1, Table 26.1.1); direct LDL: GEN 24 (6, 44) mg/dL, STB 12 (−3, 27) mg/dL ($p < 0.001$; Section 15.1, Table 26.2.1); HDL: GEN 6 (0, 12) mg/dL, STB 3 (−1, 10) mg/dL ($p = 0.046$; Section 15.1, Table 26.3.1); total cholesterol to HDL ratio: GEN 0.3 (−0.3, 0.9), STB 0.1 (−0.4, 0.6) ($p = 0.004$; Section 15.1, Table 26.4.1); triglycerides: GEN 28 (−5, 65) mg/dL, STB 13 (−21, 51) mg/dL ($p = 0.005$; Section 15.1, Table 26.5.1). For 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 in fasting glucose were as follows: GEN 3 (−3, 10) mg/dL; STB 3 (−5, 9) mg/dL ($p = 0.67$; Section 15.1, Table 26.6.1).

In general, graded laboratory abnormalities related to lipid parameters were more common in the GEN group compared with the STB group. The majority of laboratory abnormalities related to lipid parameters were Grade 1 or 2. Grade 3 LDL abnormalities were reported as follows: GEN 12.7%, 53 of 417 subjects; STB 5.0%, 21 of 417 subjects). No Grade 4 LDL abnormalities were reported in either treatment group. All other Grade 3 or 4 abnormalities related to lipid parameters were infrequent, and reported for similar percentages of subjects in each treatment group (Section 15.1, Tables 21.1 and 22.1).

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 119 subjects in the STB→GEN group, median exposure to OL GEN was 23.4 weeks (Section 15.1, Table 5.2).

Adverse Events

Among the subjects in the STB→GEN group, 42.0% of subjects (50 of 119 subjects) had any AE (Section 15.1, Table 11.2). The most commonly reported AEs that occurred in > 2 subjects during the OL Extension Phase were as follows (Section 15.1, Table 12.2):

- STB→GEN group — nasopharyngitis (4.2%, 5 subjects) and cough, LDL increased, or syphilis (each 2.5%, 3 subjects)

In the STB→GEN group during the OL Extension Phase, the majority of the AEs reported were Grade 1 or 2 (Section 15.1, Table 11.2). No Grade 4 AEs were reported, and Grade 3 AEs were reported for 7 subjects (5.9%; Section 15.1, Table 14.2). The percentage of subjects that had any AE considered related to study drug by the investigator was low (6.7%, 8 subjects). The majority of AEs considered related to study drug by the investigator were Grade 1 or 2. One subject (0.8%) reported a Grade 3 AE of nephrolithiasis that was considered related to study drug by the investigator (Section 15.1, Table 17.2).

Serious adverse events were reported for 1.7% of subjects (2 subjects) in the STB→GEN group during the OL Extension Phase; none of the events were considered related to study drug by the investigator. No additional deaths or AEs leading to discontinuation of study drug were reported in the STB→GEN group during the OL Extension Phase (Section 15.1, Table 11.2).

Bone Safety

Two subjects in the STB→GEN group had bone AEs that were considered related to study drug by the investigator (osteopenia and osteoporosis [1 subject each]). Both events were Grade 2 in severity and nonserious (Appendix 16.2, Listing 17). No subject had a bone SAE or discontinued study drug due to a bone AE during the OL Extension Phase (Section 15.1, Tables 18.2 and 20.2).

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 0.067% (3.0983%)
- **Spine:** STB→GEN 1.212% (2.8808%)

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). One subject reported a nonserious Grade 3 renal AE of nephrolithiasis that was considered related to study drug by the investigator. This AE was ongoing at the time of this report, and study drug was not interrupted for this subject (Appendix 16.2, Listing 18).

A small decrease from OL baseline in mean serum creatinine was observed in the STB→GEN group (Section 15.1, Table 28.2). The mean (SD) change from OL baseline in serum creatinine at Week 24 of the OL Extension Phase was −0.01 (0.113) mg/dL.

An increase from OL baseline in median $eGFR_{CG}$ was observed in the STB→GEN group (Section 15.1, Table 29.2). The median (Q1, Q3) change from OL baseline in $eGFR_{CG}$ at Week 24 of the OL Extension Phase was 3.6 (−4.8, 11.1) mL/min.

A decrease from OL baseline in median UPCR was observed in the STB→GEN group (Section 15.1, Table 30.4.2). The median (Q1, Q3) percentage change from OL baseline at Week 24 of the OL Extension Phase was −16.4% (−47.9%, 53.3%).

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 (Section 15.1, Tables 30.2.2 and 30.3.2). Median (Q1, Q3) percentage changes from OL baseline at Week 24 of the OL Extension Phase were as follows: urine RBP to creatinine ratio: −10.0% (−47.4%, 18.5%); urine beta-2-microglobulin to creatinine ratio: −18.8% (−73.9%, 37.1%).

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. Generally, the 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 74.8% of subjects (86 of 115 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 22.6% of subjects (26 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) and glucose. 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: 19 (3, 35) mg/dL (Section 15.1, Table 26.1.2); direct LDL: 11 (1, 27) mg/dL (Section 15.1, Table 26.2.2); HDL: 5 (−2, 10) mg/dL (Section 15.1, Table 26.3.2); total cholesterol to HDL ratio: 0.1 (−0.3, 0.5) (Section 15.1, Table 26.4.2); triglycerides: 5 (−21, 38) mg/dL (Section 15.1, Table 26.5.2); and glucose: 3 (−3, 8) mg/dL (Section 15.1, Table 26.6.2).

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 = E at Week 156: GEN 96.9%, STB 97.2%, difference in percentages: −0.5% (95% CI: −3.2%, 2.3%); M = E at Week 168: GEN 97.3%, STB 96.2%, difference in percentages: 1.4% (95% CI: −2.4%, 5.3%). Both groups had increases from baseline in mean CD4 cell counts at Week 168 (GEN 332 cells/μL; STB 310 cells/μL).
- GEN was better tolerated than STB, with lower rates of AEs considered related to study drug and AEs leading to premature 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 compared with subjects who received STB
  - No cases of proximal renal tubulopathy (including Fanconi syndrome), and no renal and urinary disorder or associated investigation AEs leading to discontinuation of study drug in the GEN group compared with 4 renal and urinary disorder or associated investigation AEs leading to discontinuation of study drug, including 1 case of acquired Fanconi syndrome (indicative of proximal renal tubulopathy), in the STB group
  - Less increase in serum creatinine and less decrease in $eGFR_{CG}$ in subjects who received GEN compared with subjects who received STB
  - Decreases in proteinuria by quantitative assessment (UPCR) in subjects who received GEN compared with subjects who received STB
  - Decreases (urine beta-2-microglobulin to creatinine ratio) or less increases (urine RBP to creatinine ratio) in renal tubular proteinuria in subjects who received GEN compared with subjects 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 AEs leading to premature discontinuation of study drug.
- 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.