FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3 Open-Label Study to Evaluate Switching from Optimized Stable Antiretroviral Regimens Containing Darunavir to Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) plus Darunavir (DRV) in Treatment Experienced HIV-1 Positive 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-292-0119
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	111007 2013-003377-93
ClinicalTrials.gov Identifier:	NCT01968551
Study Start Date:	03 September 2013 (First Subject Screened)
Study End Date:	09 July 2016 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Gregory Huhn, MD, MPHTM Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Scott McCallister, MD Telephone: PPD Fax: PPD
Report Date:	31 October 2016
Previous Report Date(s):	23 September 2015 (Interim Week 48)

STUDY SYNOPSIS

Study GS-US-292-0119

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

Title of Study: A Phase 3 Open-Label Study to Evaluate Switching from Optimized Stable Antiretroviral Regimens Containing Darunavir to Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) plus Darunavir (DRV) in Treatment Experienced HIV-1 Positive Adults

Investigators: Multicenter

Study Centers: Subjects were enrolled in a total of 63 study centers: 56 in the United States (US) and 7 in Canada.

Publications:

Publications and public presentation based on this study available at the time of this clinical study report (CSR) include the following:

Greg Huhn, Pablo Tebas, Joel Gallant et al. Strategic Simplification: the Efficacy and Safety of Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Plus Darunavir (DRV) in Treatment-Experienced HIV-1–Infected Adults (NCT01968551). IDWeek; 2015 San Diego, CA Oct. 7-11.

Huhn GD, Tebas P, Gallant J, et al. A Randomized, Open-label Trial to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide plus Darunavir in Treatment-Experienced HIV-1 Infected Adults. J Acquir Immune Defic Syndr 2016. (in press)

Study Period:

03 September 2013 (First Subject Screened)
06 July 2016 (Last Subject Observation)

Phase of Development: Phase 3

Objectives:

Study GS-US-292-0119 was conducted to assess the safety and efficacy of a regimen simplification of GEN plus DRV relative to continuing current antiretroviral (ARV) regimen in HIV-infected, virologically suppressed adult subjects with 2-class resistance and at least 2 prior regimen failures.

The primary objective of this study was as follows:

- To evaluate the efficacy of GEN fixed-dose combination (FDC) plus DRV relative to current ARV regimens in virologically suppressed, HIV-infected subjects with HIV-1 RNA < 50 copies/mL at Week 24

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of the 2 treatment groups over 24 and 48 weeks
- To evaluate the efficacy of the 2 treatments groups with HIV-1 RNA < 50 copies/mL at Week 48

The primary and secondary objectives were previously presented in the Interim CSR for this study. The current CSR provides all data available through the end of the study for all subjects who received E/C/F/TAF+DRV in the open-label phase (up to the Week 48 visit) or in the open-label Extension Phase (post Week 48 visit).

Throughout the text of this document, EVG/FTC/COBI/TAF is referred to as GEN. The designations EVG/FTC/COBI/TAF, E/C/F/TAF, and ECF/TAF are used in preprogrammed tables, figures, and listings and to describe the All E/C/F/TAF analysis sets.

Methodology:

This study was an open-label, multicenter study that consisted of 2 cohorts:

Cohort 1:

Subjects received a FDC tablet of GEN 150/150/200/10 mg + DRV 800 mg once daily with food (target n = 20).

At Week 4, safety and efficacy data from the subjects enrolled in Cohort 1 were reviewed by Gilead Sciences, Inc. (Gilead) prior to randomizing subjects into Cohort 2. Cohort 1 subjects continued treatment with GEN+DRV through 48 weeks.

Cohort 2:

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

- **Treatment Group 1:** FDC tablet of GEN 150/150/200/10 mg + DRV 800 mg once daily with food (target n = 100)
- **Treatment Group 2:** Stay on baseline DRV-containing regimen (Stay on Baseline Regimen [SBR]) (target n = 50)

After Week 48, all subjects who remained virologically suppressed were given the option to participate in the open-label Extension Phase to receive GEN in addition to DRV and attend study visits every 12 weeks until GEN became commercially available. Subjects who declined participation in the open-label Extension Phase were required to complete a 30-day follow-up visit**.**

Throughout this report, "Open-label Phase" refers to the initial 48 week comparative study period and "Extension Phase" refers to the period after the Week 48 visit in which all subjects were receiving GEN+DRV.

Number of Subjects (Planned and Analyzed):

Planned:

Approximately 170 subjects total (Cohort 1: 20 subjects; Cohort 2: 150 subjects randomized in a 2:1 ratio to GEN+DRV or SBR)

Analyzed in Extension Phase (by analysis set):

	Cohort 1 or 2 Treatment Assignment		
	GEN+DRV (112)	SBR (46)	Total
Subjects Enrolled	112	46	158
Subjects in Safety Analysis Set	110 (98.2%)	46 (100.0%)	156 (98.7%)
All E/C/F/TAF Full Analysis Set (FAS)	109 (97.3%)	34 (73.9%)	143 (90.5%)
All E/C/F/TAF Safety Analysis Set	110 (98.2%)	34 (73.9%)	144 (91.1%)

The denominator for percentages is based on the number of subjects in the All Enrolled Analysis Set.
Subject PPD in Cohort 1 did not stop taking etravirine for approximately 84 weeks while taking study drug and was excluded from the All E/C/F/TAF FAS.
A subject must have received as least 1 dose of GEN+DRV during either the open-label phase or the extension phase to be included in the All E/C/F/TAF analysis sets. All subjects received GEN+DRV in the Extension Phase.
Source: Section 15.1, Table 3

Diagnosis and Main Criteria for Inclusion: Subjects eligible for the study were HIV-infected adults with a history of ≥ 2 prior ARV regimens and resistance to ≥ 2 different classes of ARV agent; who were virologically suppressed (plasma HIV-1 RNA < 50 copies/mL) on the current ARV regimen containing DRV (600 mg twice daily or 800 mg once daily) continuously for ≥ 4 months; with plasma HIV-1 RNA < 50 copies/mL at screening; and estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula ($eGFR_{CG}$). Subjects eligible for the Extension Phase were those who had completed the initial study phase through Week 48 and remained virologically suppressed at the Week 48 time point.

Duration of Treatment: 48 weeks of study drug treatment followed by an optional open-label Extension Phase in which all subjects receive GEN+DRV until GEN became commercially available.

Test Product, Dose, Mode of Administration, and Lot No.:

Fixed-dose combination tablet of GEN (150/150/200/10 mg) administered orally once daily with food at approximately the same time plus DRV (600 mg) administered orally twice daily or DRV (800 mg) administered orally once daily. DRV (800 mg) was provided by Gilead.

Lot Numbers:

GEN: CP1209B1, CP1307B1, CP1313B1, CP1315B1, CP1403B1, and CP1503B1

DRV (800 mg): 13KG470, 13LG539, 14CG967, 14GG212, and FDZ0L00

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

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was the percentage of subjects in Cohort 2 with HIV-1 RNA < 50 copies/mL at Week 24 as defined by the US Food and Drug Administration (FDA)-defined snapshot algorithm. Secondary efficacy endpoints included the percentage of subjects in Cohort 2 with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm, the percentage of subjects in Cohort 2 with HIV-1 RNA < 20 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm, the change from baseline in CD4 cell count at Weeks 24 and 48 for the Open-label Phase and All E/C/F/TAF Analyses, the time to pure virologic failure with HIV 1 RNA cutoff at 50 copies/mL by Week 48 for the Open-label Phase Analysis, the percentage of subjects in Cohort 2 with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by 2 different missing data imputation methods (missing = excluded [M = E] and missing = failure [M = F]) for the Open-label Phase analysis, and the percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the M = E data imputation method for the All E/C/F/TAF Analysis. Analyses for these primary and secondary efficacy endpoints through the Week 48 time point were provided in the Interim CSR.

The secondary efficacy endpoints analyzed for this final-analysis CSR were the proportion of subjects with HIV-1 RNA < 50 copies/mL at all assessed visits (defined by M = E data imputation method) and the change from baseline in CD4 cell count at all assessed visits.

Pharmacokinetics:

All PK assessments were performed and summarized for the Interim CSR and were not repeated for this final-analysis CSR.

Safety:

Safety assessments for this final-analysis CSR included adverse event (AE) reviews, complete or symptom-directed physical examinations, vital signs, laboratory analyses (hematology, chemistry, and urinalysis) for study visits including those during the Extension Phase.

Other:

All results from visual analog scale (VAS) adherence questionnaires, HIV treatment satisfaction questionnaire (HIV-TSQ), and Short Form-36 (SF-36) were summarized in the Interim CSR. Biomarker analyses of blood and urine samples (RBP, Beta-2-microgrobulin) were analyzed as part of the interim CSR.

Statistical Methods:

Efficacy:

For this final-analysis CSR, the efficacy analysis used the All E/C/F/TAF FAS, which included all subjects who received at least one dose of study medication during the open-label phase or the Extension Phase of the study.

Efficacy data were summarized for all subjects in the All E/C/F/TAF FAS by treatment group as assigned during the Open-label Phase and overall.

Virologic response defined as maintaining HIV-1 RNA < 50 copies/mL was analyzed by using the M = E method for imputing missing HIV-1 RNA values. In this approach, all missing data were excluded in the computation of virologic response (ie, missing data points excluded from both the numerator and denominator in response rate).

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL and HIV-1 RNA ≥ 50 copies/mL were summarized at all assessed visits for all subjects in the All E/C/F/TAF FAS. The proportion of subjects with HIV-1 RNA < 20 copies/mL and not detectable, and HIV-1 RNA < 20 copies/mL and detectable, and HIV-1 RNA < 50 and ≥ 20 copies/mL were summarized separately.

The analysis of CD4 cell count was based on on-treatment data (ie, data collected up to 1 day after the last dose date of study drug). The baseline value was defined based on the Study Day 1 for the Extension Phase for subjects who switched to GEN from SBR in the Extension Phase. For all other subjects, the baseline value was based on Study Day 1 for the initial open-label phase.

The changes from baseline in CD4 cell count at all assessed visits were summarized using descriptive statistics based on observed data (ie, missing data excluded) for all subjects in the All E/C/F/TAF FAS.

The mean and 95% CI of change from baseline in CD4 cell count over time were plotted using observed data for All E/C/F/TAF analysis.

Pharmacokinetics:

No PK assessments were performed for this report.

Safety:

The All E/C/F/TAF Safety Analysis Set included all subjects who received at least one dose of study medication during the initial open-label phase or the Extension Phase of the study.

Safety data were summarized for all subjects in the All E/C/F/TAF Safety Analysis Set by treatment group as assigned during the open-label phase and overall, unless specified otherwise.

The baseline value was defined based on the Study Day 1 for the Extension Phase for the subjects who switched to GEN from SBR in the Extension Phase. For all other subjects, baseline value was based on Study Day 1 for the initial open-label phase.

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

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 158 subjects were enrolled in the study, of whom 156 received at least 1 dose of study drug (Cohort 1 21 subjects; Cohort 2 GEN+DRV 89 subjects; Cohort 2 SBR 46 subjects) (Section 15.1, Table 2.1).

Of the 21 enrolled and treated subjects in Cohort 1, 20 subjects completed study drug through Week 48 and 1 prematurely discontinued study drug prior to Week 48 due to withdrawal of consent. All 20 subjects (95.2%) who completed study drug through Week 48 entered the Extension Phase.

Of the 135 enrolled and treated subjects in Cohort 2 (GEN+DRV 89 subjects; SBR 46 subjects), 128 subjects completed study drug through Week 48, and 7 subjects prematurely discontinued study drug prior to Week 48: 2 subjects (2.2%) in the GEN+DRV group and 5 subjects (10.9%) in the SBR group. Of the 7 subjects who prematurely discontinued, 4 subjects withdrew consent (GEN+DRV 1 subject; SBR 3 subjects), 2 subjects were lost to follow-up (both SBR), and 1 subject discontinued at investigator's discretion (GEN+DRV). Seven subjects who completed through Week 48 in the initial open-label phase elected not to continue beyond that time point. Thus, 121 subjects from Cohort 2 (GEN+DRV 87 subjects [97.8%]; SBR 34 subjects [73.9%]) entered the Extension Phase.

Combined, a total of 141 subjects from Cohorts 1 and 2 entered the study Extension Phase (107 of whom remained on GEN+DRV from the initial open-label phase and 34 of whom switched from SBR to GEN+DRV [hereafter referred to as "SBR→E/C/F/TAF+DRV"]; Section 15.1, Table 2.2). Of these 141 subjects, 6 prematurely discontinued study drug during the Extension Phase (GEN+DRV 2 subjects [1.8%]; SBR→E/C/F/TAF+DRV 4 subjects [11.8%]). In the GEN+DRV group, 1 subject discontinued due to death and 1 subject was lost to follow-up. In the SBR→E/C/F/TAF+DRV group, 2 subjects discontinued study drug due to AE, 1 subject withdrew consent, and 1 subject was lost to follow-up. A subject narrative for the discontinuation due to death is provided in Section 15.2. Subject narratives for the AEs leading to discontinuation of study drug were provided in the Interim CSR.

Demographics and baseline characteristics of subjects who entered the Extension Phase were consistent with those of the overall study population. Most subjects in the All E/C/F/TAF Safety Analysis Set were male (73.6%), with a median age of 50 years (range: 26 to 70); most were white (50.7%) or black (45.1%), and a majority were non-Hispanic/Latino (86.8%) (Section 15.1, Table 4). The median (Q1, Q3) body mass index (BMI) at baseline was 27.4 (24.7, 32.1) kg/m^2 (range, 18.7 to 53.7).

Baseline disease characteristics of subjects who entered the Extension Phase were consistent with those of the overall study population (Section 15.1, Table 5). Most subjects were virologically suppressed at baseline, as evidenced by the percentage of subjects who had HIV-1 RNA < 50 copies/mL (137 of 144 subjects [95.1%]). The overall median (Q1, Q3) baseline CD4 cell count was 536 (397, 744) cells/μL, the overall median (Q1, Q3) baseline CD4% was 27.4% (20.9%, 33.5%), and the most common HIV risk factor categories were homosexual sex (54.9%) and heterosexual sex (38.9%). Most subjects (84.0%) had no proteinuria (Grade 0 by dipstick) on urinalysis, and the median (Q1, Q3) $eGFR_{CG}$ was 102.0 (79.9, 122.5) mL/min. Hyperlipidemia was reported for 45.8% of subjects, hypertension was reported for 38.2% of subjects, diabetes mellitus was reported for 9.7% of subjects, and cardiovascular disease was reported for 6.3% of subjects.

Efficacy Results:

High rates of virologic suppression were maintained in the Extension Phase in both treatment groups through a maximum of 132 weeks of GEN+DRV treatment in the GEN+DRV group and through a maximum of 72 weeks of GEN+DRV treatment in the SBR→GEN+DRV group. The percentages of subjects with HIV-1 RNA < 50 copies/mL (M = E method) were as follows for selected time points: Week 96 for GEN+DRV 96.6% (84 of 87 subjects); Week 48 for SBR→GEN+DRV 92.0% (23 of 25 subjects) (Section 15.1, Table 9). CD4 cell counts remained stable on treatment for both treatment groups (Section 15.1, Table 10).

Resistance Testing Results:

A cumulative assessment of all resistance testing for the study is summarized below. Details for resistance testing through the Week 48 time point are provided in a separate Virology Study Report (PC-120-2026).

Baseline: Historical Genotypes

HIV-1 genotyping was not conducted prestudy, because all subjects who enrolled in this study had HIV RNA < 50 copies/mL at screening. However, review of historical genotypic reports for the PR/RT genes (from several different genotyping assays) was conducted in real-time prior to enrollment (PC-120-2026). Most subjects had documented resistance to at least 2 classes of ARV drugs (n = 128; 94.8%; Appendix 16.2, Virology Listing 1); a summary is provided below.

Baseline: Preexisting Resistance

The distribution of pretreatment ARV resistance mutations was comparable between the 2 treatment groups. The most common ARV resistance class was the nucleoside reverse transcriptase (RT) inhibitor (NRTI) class (n = 128; 94.8%), followed by the non-nucleoside RT inhibitor (NNRTI) class (n = 119; 88.1%), and the protease inhibitor (PI) class (n = 47; 34.8%).

Within the NRTI resistance class, the 2 most common mutations were M184V/I (n = 112; 83%) and K65R (n = 32; 23.7%). Thymidine analogue mutations (TAMs) in RT were found in 57 subjects (42.2%) across all historical genotypic reports. The distribution of TAMs was comparable across treatment groups.

Subjects Experiencing Virologic Failure

On-treatment virologic failure was determined based on the US FDA-defined snapshot algorithm. Seven subjects (2 in the GEN+DRV group, and 5 in the SBR group) had HIV-1 RNA > 50 copies/mL at Week 48, and were classified as virologic failures (Resistance Analysis Population is reported in PC-120-2026, Virology Study Report).

Development of Resistance in Subjects With Unconfirmed Virologic Failure

Six of the 7 subjects with virologic failure (Subjects PPD and PPD in the GEN+DRV group; and Subjects PPD PPD PPD and PPD in the SBR group) experienced a transient virologic rebound, with HIV-1 RNA < 400 copies/mL before re-suppressing HIV-1 RNA < 50 copies/mL at the subsequent visit, and did not meet the criteria for resistance analyses.

Development of Resistance in Subjects With Confirmed Virologic Failure - Resistance Analysis Population

One subject (Subject PPD in the SBR group) experienced confirmed virologic rebound with HIV-1 RNA > 400 copies/mL in the initial open-label phase and was analyzed for resistance. This subject developed the RT mutation M184V with phenotypic resistance against FTC and 3TC; the PR mutations L33F, M46I, I50V, and V82A with phenotypic resistance against DRV, AMP, and LPV; and the RT mutations K65K/R and E138G with no phenotypic resistance to either TFV or ETR. The RT mutations that were present in the historical genotypic report (D67N, K70R, K103N, Y181I, T215Y; dated December 2002) were no longer detected at virologic failure (March 2015) (Appendix 16.2, Virology Listing 2 and Virology Listing 3).

Pharmacokinetic/Pharmacodynamic Results:

No PK/PD assessments were performed for this report.

Safety Results:

In the GEN+DRV group, the median (Q1, Q3) exposure to GEN+DRV was 98.1 (89.4, 108.1) weeks (Section 15.1, Table 6). In the SBR→E/C/F/TAF+DRV group, the median (Q1, Q3) exposure to GEN+DRV was 47.9 (44.1, 56.4) weeks. Study drug adherence was high in both groups; the median (Q1, Q3) adherence rate was 97.8% (94.5, 99.1) in the GEN+DRV group and 97.1% (93.0, 99.0) in the SBR→E/C/F/TAF+DRV group (Section 15.1, Table 8).

Adverse Events

As described in the methods above, for subjects in the SBR→GEN+DRV group (ie, those who switched from SBR to GEN+DRV at the start of the Extension Phase), treatment-emergent AEs included only AEs that started after the first dose date of GEN+DRV. Thus, events that started in the initial open-label phase (while these subjects were receiving SBR) were excluded from AE analyses for this group. In contrast, AE assessments for the GEN+DRV group comprised all treatment-emergent events, including those that started after the first dose in either the initial open-label phase or the Extension Phase. For simplicity, the text herein will focus primarily on the combined totals for GEN+DRV-exposed subjects assessed from the All E/C/F/TAF Safety Analysis Set.

Accounting for differences in exposure, results for the All E/C/F/TAF Safety Analysis Set were consistent with those reported for the GEN+DRV group overall in the interim CSR. Most subjects (91.0%; 131 of 144 subjects) in the All E/C/F/TAF Safety Analysis Set had at least 1 AE (Section 15.1, Table 11). The majority of the AEs reported were Grade 1 or Grade 2 in severity. Grade 3 or 4 AEs were reported for 13.2% of subjects (19 subjects); however, only 2.8% subjects (4 subjects) had a Grade 3 or 4 AE considered related to study drug by the investigator. Serious adverse events were reported for 13.9% of subjects (20 subjects); 1 subject (PPD in the GEN+DRV group) had an SAE (subdural hematoma [in the setting of concomitant warfarin use]) considered related to study drug by the investigator (Appendix 16.2, Listing 1 and Listing 19.2). The event occurred on Day 417 and resolved on Day 495 (it was not reported in the interim CSR). Two subjects, both of whom were in the SBR→GEN+DRV group, reported AEs that led to premature study drug discontinuation; both events were reported in the Interim CSR; thus, no additional subjects discontinued study drug due to AEs during the Extension Phase (Appendix 16.2, Listing 20). Two subjects in the GEN+DRV group died (Appendix 16.2, Listing 22). Both deaths were previously reported in the Interim CSR; 1 death occurred during the initial open-label phase and 1 occurred during the Extension Phase. Subject narratives for AEs that led to study drug withdrawal, SAEs, and deaths are provided in Section 15.2 of this report.

No additional Centers for Disease Control (CDC) Class C AIDS-defining events were reported since the time of the Interim CSR (Appendix 16.2, Listing 21).

The most common AEs in the All E/C/F/TAF Safety Analysis Set were as follows: upper respiratory infection (18.8%, 27 subjects), headache (11.1%, 16 subjects), and bronchitis and sinusitis (10.4%, 15 subjects) (Section 15.1, Table 12). The most common AEs considered related to GEN+DRV by the investigator were nausea (2.1%, 3 subjects) and abnormal dreams, dyspepsia, fatigue, migraine, and vomiting (each 1.4%, 2 subjects) (Section 15.1, Table 15).

Bone Safety

Three fractures occurred in the All E/C/F/TAF Safety Analysis Set. All reported fracture events were the result of trauma and considered not related to study drug by the investigator; none were indicative of fragility fractures and none resulted in permanent discontinuation of study drug. Two of the 3 fracture events were reported in the Interim CSR. The additional fracture event occurred during the Extension Phase (Subject PPD GEN+DRV group; Grade 2 traumatic rib fracture [reported as an SAE]; Section 15.1, Table 26 and Appendix 16.2, Listing 18). Median (Q1, Q3) percentage changes from baseline in parathyroid hormone (PTH), a hormone involved in bone metabolism, were as follows: Week 48: 5.5% (−12.2%%, 39.9%; n = 102); Week 96: 6.2% (−13.5%, 49.3%; n = 79; Section 15.1, Table 25.23). Narratives for all fracture events are provided in Section 15.2.

Renal Safety

No renal SAEs, AEs of proximal renal tubulopathy, or discontinuations due to renal AEs were reported during the study in either treatment group (Section 15.1, Table 12, Table 18, and Table 20). Changes from baseline in serum creatinine or eGFR (by CG or CKD-EPI, creatinine equations) were minimal throughout the study in the All E/C/F/TAF Safety Analysis Set (Section 15.1, Table 27, Table 28.1, and Table 28.2). Grade 1 or 2 proteinuria by urinalysis was reported for 25% of subjects across both treatment groups (36 of 144 subjects); no subject had Grade 3 proteinuria (Section 15.1, Table 21). Quantitative total proteinuria (urine protein to creatinine ratio [UPCR]) decreased from baseline in the All E/C/F/TAF Safety Analysis Set (Section 15.1, Table 29). Median (Q1, Q3) percent changes from baseline were as follows: Week 48: −23.6% (−44.4%, 5.6%; n = 129); Week 96: −11.5% (−42.5%, 19.9%; n = 77).

Cardiovascular Events

For the All E/C/F/TAF Safety Analysis Set, AEs in the SOC of Cardiac Disorders were reported for 4.9% of subjects (7 subjects) (Section 15.1, Table 12). Five SAEs in the SOC of Cardiac Disorders (angina pectoris, angina unstable, coronary artery disease, myocardial infarction, and tachycardia) were reported among 3 subjects (Section 15.1, Table 18); all were in the GEN+DRV group, and all had medical history indicating preexisting coronary artery disease (ie, Subjects PPD [SAE of coronary artery disease] and PPD [SAEs of angina pectoris, unstable angina, and myocardial infarction) or other etiologies, eg, substance abuse/withdrawal (Subject PPD [SAE of tachycardia]). None of these events was considered related to study drug by the investigator (Section 15.1, Table 19). Subject narratives for the SAEs are provided in Section 15.2 of this report.

Laboratory Abnormalities

A total of 129 subjects (89.6%) in the All E/C/F/TAF Safety Analysis Set had at least 1 laboratory abnormality reported during the study, and most of these were Grade 1 or Grade 2 in severity; Grade 3 or 4 laboratory abnormalities were reported for 14.6% of subjects (21 subjects) (Section 15.1, Table 21). The most common Grade 3 or 4 laboratory abnormalities (excluding nonfasting serum glucose) in the All E/C/F/TAF Safety Analysis Set were creatine kinase (4.9%, 7 subjects), serum amylase (2.8%, 4 subjects), and low neutrophil counts (2.1%, 3 subjects) (Section 15.1, Table 22). For liver enzyme elevations in relation to normal ranges, no subjects had AST or ALT > 3 × the upper limit of normal (ULN) and total bilirubin > 1.5 × ULN (Section 15.1, Table 23). Evaluation of laboratory data demonstrated that no potential Hy's Law

cases were identified. Summaries of laboratory findings by study visit are provided for hematology parameters in Section 15.1, Table 24.1 to Table 24.13 and for serum chemistry analytes in Section 15.1, Table 25.1 to Table 25.24.

CONCLUSIONS:

The conclusions from the final analysis of Study GS-US-292-0119 in virologically suppressed HIV-infected subjects with documented resistance to 2 or more classes of ARV agents who switched to GEN+DRV from an optimized stable ARV regimen containing DRV (SBR) are largely unchanged from the prior analyses reported through Week 48 and are as follows:

- A high rate of virologic suppression was maintained with dosing through a maximum duration of GEN+DRV dosing of 132 weeks.
- The most common pre-treatment ARV resistance class observed in the study was from the NRTI class (94.8%), followed by the NNRTI class (88.1%), and the PI class (34.8%). The distribution of pretreatment ARV resistance mutations was comparable between the 2 treatment groups. No subject from the GEN+DRV group experienced confirmed virologic rebound through 96 weeks of treatment in the study. The resistance analysis population (RAP) included 1 subject from the SBR group with confirmed virologic rebound in the initial open-label phase.
- GEN+DRV was safe and well-tolerated, with low rates of study drug discontinuations due to AEs, treatment-related Grade 3 or 4 AEs, and SAEs. There were no renal SAEs or AEs of proximal renal tubulopathy reported, and no discontinuations due to renal AEs occurred during the study.