FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Abacavir/Lamivudine (ABC/3TC) plus a Third Antiretroviral Agent to the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects
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. Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-292-1823
Phase of Development:	Phase 3b
IND No.:	111007
EudraCT No.:	2015-002711-15
ClinicalTrials.gov Identifier:	NCT02605954
Study Start Date:	18 November 2015 (First Subject Screened)
Study End Date:	14 June 2017 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Giuliano Rizzardini Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Richard Haubrich, MD Telephone: PPD Fax: PPD
Report Date:	23 May 2018

STUDY SYNOPSIS

Study GS-US-292-1823

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

Title of Study: A Phase 3b, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Abacavir/Lamivudine (ABC/3TC) plus a Third Antiretroviral Agent to the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Fixed-Dose Combination (FDC) in Virologically-Suppressed HIV-1 Infected Adult Subjects
Investigators: Multicenter study
Study Centers: 11 sites in France, 4 sites in Germany, 8 sites in Italy, 12 sites in Spain, 1 site in the United Kingdom, and 11 sites in the United States (US)
Publications: A Gori, G Rizzardini, C Miralles, J Olalla, JM Molina, F Raffi, P Kumar, A Antinori, M Ramgopal, HJ Stellbrink, M Das, H Chu, R Ram, W Garner, SK Chuck, D Piontkowsky, R Haubrich. Switching from An Abacavir (ABC)/Lamivudine (3TC)-Based Regimen to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) is Efficacious and Safe: Week 24 Primary Analysis of a Randomized Controlled Study in Virologically-Suppressed Adults [Presentation]. XVIII Congrès National de la SFLS, 19-20 October 2017, Nice Acropolis, France
Study Period: 18 November 2015 (First Subject Screened) 14 June 2017 (Last Subject Last Observation for the Primary Endpoint)
Phase of Development: Phase 3b

Objectives:

The primary objective of this study was as follows:

- To evaluate the efficacy of switching to Genvoya® (elvitegravir [EVG; E]/cobicistat [COBI; C]/emtricitabine [FTC; F]/tenofovir alafenamide [TAF]; hereafter referred to as "GEN") fixed-dosed combination (FDC) relative to continuing on a baseline regimen consisting of abacavir (ABC)/lamivudine (3TC) plus a third antiretroviral (ARV) agent in maintaining HIV-1 RNA < 50 copies/mL at Week 24 (using Food and Drug Administration [FDA] snapshot algorithm) in virologically suppressed, HIV-1 infected adult subjects

The secondary objectives of this study were as follows:

- To evaluate the proportion of subjects maintaining virological response (defined as HIV-1 RNA < 50 copies/mL, FDA snapshot analysis) at Weeks 12 and 48
- To evaluate changes from baseline in CD4 cell counts at Weeks 24 and 48
- To evaluate the safety and tolerability of the 2 treatment groups over 24 and 48 weeks

Methodology: This was a randomized, open-label, multicenter study to evaluate the safety and efficacy of switching from ABC/3TC+3rd agent to GEN in virologically suppressed, HIV-1 infected adult subjects.

Subjects were randomized in a 2:1 ratio to one of the following treatment groups. Randomization was stratified by age (< 60 years or ≥ 60 years):

- **Treatment Group 1:** Switch from ABC/3TC+3rd agent to GEN (n = 200; Treatment Group 1 is referred to as the Immediate Switch to GEN group throughout the report)
- **Treatment Group 2:** Continue on the current regimen of ABC/3TC+3rd agent for 24 weeks followed by a delayed switch to GEN (n = 100)

  Subjects who switched from ABC/3TC+3rd agent to GEN at Week 24 is referred to as the Delayed Switch to GEN group throughout the report.

After screening, study visits occurred at Day 1 and Weeks 4, 8, 12, 24, 36, and 48. Subjects in the Delayed Switch to GEN group also had a study visit at Weeks 28 and 32, which were 4 and 8 weeks after switching to the GEN FDC, respectively. Adverse events (AEs) and concomitant medications were assessed at each visit.

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

Calculated creatinine clearance, glucose, hematology, serum chemistry, urine chemistry, and urinalysis tests were performed at all visits.

Fasting lipid panel (total cholesterol, high density lipoprotein [HDL] and low density lipoproteins [LDL], and triglycerides) were collected at Day 1, and Weeks 12, 24, 36 (ABC/3TC+3rd agent group only), and 48.

Blood and urine for selected evaluations of bone and renal safety, inflammation, platelet function, and coagulation were collected at Day 1, Weeks 4, 12, 24, and 48 (all subjects) and also at Weeks 28 and 36 for subjects in the ABC/3TC+3rd agent group.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 300 subjects, with at least 40 subjects ≥ 60 years old enrolled
Analyzed: 274 subjects (226 subjects were < 60 years old and 48 subjects were ≥ 60 years old)

Analyzed (by analysis set):

	GEN	ABC/3TC+3rd Agent
Subjects in Safety Analysis Set	183	91
Subjects in Full Analysis Set (FAS)	183	91

Diagnosis and Main Criteria for Inclusion: Subjects enrolled received ABC/3TC+3rd agent for ≥ 6 consecutive months preceding the screening visit. For subjects with 3 or more ARV therapy (ART) regimens, a regimen history was provided to the Sponsor for approval. Allowed third ARV agents included lopinavir boosted with ritonavir (LPV/r), atazanavir (ATV)+ritonavir (RTV), ATV+COBI (or ATV/COBI FDC), darunavir (DRV)+RTV, DRV+COBI (or DRV/COBI FDC), fosamprenavir (FPV)+RTV, saquinavir (SQV)+RTV, ATV (no booster), efavirenz (EFV), rilpivirine (RPV), nevirapine (NVP), etravirine (ETR), raltegravir (RAL), or dolutegravir (DTG).

Subjects had to have documented plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 months preceding the screening visit (measured at least twice using the same assay) and plasma HIV-1 RNA < 50 copies/mL at screening. Subject had to have adequate renal function, defined as having an estimated glomerular filtration rate (eGFR) calculated using the Cockcroft-Gault equation (eGFRCG) of ≥ 30 mL/min.

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

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

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

Batch numbers: CP1502B1, CP1505B1, and CP1604B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: ABC/3TC (600/300 mg)+3rd agent was orally administered. Investigators provided a prescription for the treatment, and subjects were responsible for obtaining their medication prior to or during the study visit.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was as follows:

- HIV-1 RNA < 50 copies/mL at Week 24 (United States [US] FDA-defined snapshot analysis)

The secondary endpoints were as follows:

- HIV-1 RNA < 50 copies/mL at Weeks 12 and 48 (US FDA-defined snapshot analysis)
- Changes in CD4 cell count at Weeks 24 and 48

Other efficacy endpoints were as follows

- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 12, 24, and 48 as determined by the US FDA-defined snapshot algorithm.
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 as defined by 2 different missing data imputation methods (missing = excluded [M = E] and missing = failure [M = F]).
- The change from baseline in CD4% at Weeks 12, 24 and 48.

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

Safety: Adverse events and clinical laboratory tests, including bone biomarkers (parathyroid [PTH] and serum OH-25 vitamin D), fracture events, serum creatinine, $eGFR_{CG}$, proteinuria (dipstick), renal biomarkers (eg, urine protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR], urine retinol binding protein [RBP] to creatinine ratio, and beta-2-microglobulin to creatinine ratio), inflammation platelet function, and coagulation were performed.

Other: Patient reported outcomes (PROs) related questionnaires were administered, including the Adherence Visual Analogue Scale (VAS), HIV Treatment Satisfaction, EuroQoL (5 domains) (EQ-5D), Medical Outcome Study Short Form-36 (SF-36), and Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F).

Statistical Methods:

Efficacy: The Full Analysis Set (FAS) included all the subjects who were randomized and received at least 1 dose of study drug (either GEN or ABC/3TC+3rd agent on or after Day 1). The FAS was the primary analysis set for the efficacy analyses.

The primary evaluation of the FDA-defined snapshot endpoint at Week 24 was evaluated by constructing a 2-sided exact 95% confidence interval for the difference in treatment group response rates (GEN minus control) to determine if the lower bound was greater than −12%. Superiority was to be declared (p-value was calculated) if the lower bound of the 95% confidence interval is greater than 0.

Other efficacy endpoints were analyzed and were described in the Statistical Analysis Plan (SAP).

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

Safety: The Safety Analysis Set included all randomized subjects who took at least 1 dose of GEN or ABC/3TC+3rd Agent (on or after Day 1). The Safety Analysis Set was the primary analysis set for safety analyses.

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

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

Laboratory data collected during the study were analyzed and summarized using both quantitative and qualitative methods.

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

Other: Patient reported outcomes data were analyzed and summarized using both quantitative and qualitative methods. Summaries were provided for the Safety Analysis Set.

Subjects who took ABC/3TC+3rd agent for 24 weeks followed by a switch to GEN, the last dose date of ABC/3TC+3rd agent was set as the day prior to the first dose of GEN (ie, the Delayed Switch to GEN group baseline), and the first dose of GEN was Day 1 for these subjects in the Delayed Switch to GEN group.

SUMMARY OF RESULTS:

Subject Disposition: A total of 275 subjects were randomized, of which 274 subjects received at least 1 dose of the study drug (GEN 183 subjects; ABC/3TC+3rd agent 91 subjects); 1 subject randomized to ABC/3TC+3rd agent group did not receive study drug. A total of 177 subjects in the Immediate Switch to GEN group and 90 subjects in the ABC/3TC+3rd agent group completed 24 weeks of treatment. Of those 90 subjects in the ABC/3TC+3rd agent group who completed 24 weeks of treatment, 89 subjects (98.9%) switched to receive GEN after Week 24 (Delayed Switch to GEN group).

Subjects who prematurely discontinued the study drug were as follows: Immediate Switch to GEN group 18 of 183 subjects (9.8%); ABC/3TC+3rd agent group 3 of 91 subjects (3.3%). Of the 3 subjects in the ABC/3TC+3rd agent group who prematurely discontinued study drug, 1 subject discontinued study drug due to an AE after receiving 1 dose of GEN, and 2 subjects discontinued study drug due to subject's decision while receiving ABC/3TC+3rd agent (Listings 16.2.1.3 and 16.2.5.1). The most common reason for study drug discontinuation was as follows: Immediate Switch to GEN group: AEs 8 subjects (4.4%); ABC/3TC+3rd agent group: subject decision 2 subjects (2.2%) (Table 15.8.1.3).

Subject Demographics and Baseline Disease Characteristics:

The demographics and general baseline characteristics were similar between the 2 treatment groups.

Overall, the majority of subjects were male (Immediate Switch to GEN group 85.2%; ABC/3TC+3rd agent group: 81.3%), with a mean age as follows: Immediate Switch to GEN group 50 years (range 25 to 80 years); ABC/3TC+3rd agent group: 49 years (range 25 to 82 years). Most subjects were white (Immediate Switch to GEN group: 82.0%; ABC/3TC+3rd agent group: 82.4%) and not Hispanic or Latino (Immediate Switch to GEN group: 85.2%; ABC/3TC+3rd agent group: 82.0%). The mean (SD) baseline values for body mass index were as follows: Immediate Switch to GEN group 25.7 (4.49) kg/m^2; ABC/3TC+3rd agent group: 27.0 (5.63) kg/m^2 (Table 15.8.3.1).

In the Immediate Switch to GEN group, most subjects had baseline HIV-1 RNA < 50 copies/mL (177 of 183 subjects; 96.7%) and 6 of 183 subjects (3.3%) had ≥ 50 copies/mL HIV-1 RNA level. The mean (SD) CD4 cell count was 701 (280.1) cells/μL. The most common HIV risk factor category was homosexual sex (61.7%). No subject had positive hepatitis B virus surface antigen (HBsAg), and 8 subjects (4.4%) had positive hepatitis C virus (HCV) antibody. Most subjects had no proteinuria as assessed by dipstick (57.4%). The mean (SD) $eGFR_{CG}$ value was 101.7 (29.69) mL/min. Most subjects did not have a history of diabetes mellitus (94.0%), hypertension (74.3%), cardiovascular disease (96.7%), hyperlipidemia (66.7%), or familial history (mother/father/brother/sister) of myocardial infarction or stroke before the age of 50 years (84.2%).

In the ABC/3TC+3rd agent group, all subjects had baseline < 50 copies/mL HIV-1 RNA level. The mean (SD) CD4 cell count was 753 (312.8) cells/μL. The most common HIV risk factor category was homosexual sex (57.1%). No subject had positive HBsAg, and 10 subjects (11.0%) had positive HCV antibody. Most subjects had no proteinuria as assessed by dipstick (56.0%). The mean (SD) $eGFR_{CG}$ value was 106.5 (40.73) mL/min. Most subjects did not have a history of diabetes mellitus (98.9%), hypertension (74.7%), cardiovascular disease (98.9%), hyperlipidemia (61.5%), or familial history (mother/father/brother/sister) of myocardial infarction or stroke before the age of 50 years (80.2%) (Table 15.8.3.2).

Efficacy Results:

High rates of virologic suppression were achieved and maintained in both Immediate Switch to GEN and ABC/3TC+3rd agent groups at Week 24. The percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 24, as determined by the US FDA-defined snapshot algorithm, were similar for both the Immediate Switch to GEN and ABC/3TC+3rd agent groups (Immediate Switch to GEN group: 93.4% [171 of 183 subjects]; ABC/3TC+3rd agent group: 97.8% [89 of 91 subjects]; difference in percentages: −4.4, 95% CI: −9.4% to 1.9%). Because the lower bound of the 2-sided 95% CI of the difference between the 2 treatment groups (Immediate Switch to GEN - ABC/3TC+3rd agent groups) was greater than the prespecified −12% margin, GEN was determined to be noninferior to ABC/3TC+3rd agent.

In the Immediate Switch to GEN group, 2 subjects (1.1%) had HIV-1 RNA ≥ 50 copies/mL and 10 subjects (5.5%) had no virologic data at Week 24. Of the 2 subjects who had HIV-1 RNA ≥ 50 copies/mL, 1 subject was withdrawn due to poor adherence and the other withdrew their consent on Day 1, after receiving the first GEN dose (Table 15.9.1.1). For the subject who had poor adherence, the investigator discontinued study drug due to poor adherence at Week 15. The overall adherence for this subject was 84.8% (Listing 16.2.5.3). In addition, treatment-emergent M184V and N155H mutations were identified conferring 3TC, FTC, EVG, and RAL resistance (Phenosense GT, GeneSeq, and PhenoSense IN). HIV virus remained susceptible to TAF, ABC,

DTG, and bictegravir. For the subject who withdrew consent on Day 1, after receiving the first GEN dose; the HIV-1 RNA levels for this subject were as follows: screening 33 copies/mL; Day 1 (predose) 110 copies/mL (Listing 16.2.6). After switching to GEN for 24 weeks in the Delayed Switch to GEN group, a high rate of virologic suppression was maintained (Week 24: 96.6% [86 of 89 subjects]) (Table 15.9.1.1).

Similar results were observed at both Weeks 12 and 48. At Week 12, the percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL, as determined by the US FDA-defined snapshot algorithm, were similar for both the Immediate Switch to GEN and ABC/3TC+3rd agent groups (Immediate Switch to GEN group: 95.1% [174 subjects]; ABC/3TC+3rd agent group: 98.9% [90 subjects]; difference in percentages: −3.8%, 95% CI: −8.3% to 1.6%). After switching to GEN for 12 weeks in the Delayed Switch to GEN group, high rates of virologic suppression were maintained (Week 12: 96.6% [86 subjects]) (Table 15.9.2.1).

At Week 48, 86.9% (159 subjects) of the subjects who were randomized to the Immediate Switch to GEN group had HIV-1 RNA < 50 copies/mL. As described above, 2 subjects with HIV-1 RNA > 50 copies/mL discontinued GEN due to consent withdrawal and poor adherence; in addition, 22 subjects (12.0%) did not have on-treatment virologic data in the Week 48 window for the following reasons: 8 subjects (4.4%) discontinued study drug due to AE and the last available HIV-1 RNA was < 50 copies/mL (1 additional subject compared with Week 24), 8 subjects (4.4%) discontinued study drug due to other reasons, and 6 subjects (3.3%) had missing data due to no HIV-1 RNA data at the Week 48 window after discontinuation of study drug (Table 15.9.2.2).

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the M = F and M = E methods for the Immediate Switch to GEN, ABC/3TC+3rd agent, and Delayed Switch to GEN groups at Weeks 12, 24, and 48 were as follows:

M = F

- Immediate Switch to GEN group: Week 12: 98.4% (180/183 subjects); Week 24: 96.7% (177/183 subjects); Week 48: 92.9% (170/183 subjects)
- ABC/3TC+3rd agent group: Week 12: 98.9% (90/91 subjects); Week 24: 97.8% (89/91 subjects)
- Delayed Switch to GEN group: Week 12: 96.6% (86/89 subjects); Week 24: 98.9% (88/89 subjects) (Table 15.9.3.4)

M = E

- Immediate Switch to GEN group: Week 12: 99.4% (180/181 subjects); Week 24: 100.0% (177/177 subjects); Week 48: 99.4% (170/171 subjects)
- ABC/3TC+3rd agent group: Week 12: 100.0% (90/90 subjects); Week 24: 100.0% (89/89 subjects)
- Delayed Switch to GEN: Week 12: 100.0% (86/86 subjects); Week 24: 100.0% (88/88 subjects) (Table 15.9.3.5)

The mean (SD) baseline CD4 cell counts were as follows: Immediate Switch to GEN group: 701 (280.1) cells/µL; ABC/3TC+3rd agent group: 753 (312.8) cells/µL; Delayed Switch to GEN group: 762 (320.5) cells/µL. For the Immediate Switch to GEN group, a mean (SD) decrease from baseline was observed at Week 4 (−34 [145.0] cells/µL), which was stable through Weeks 24 (−28 [161.4] cells/µL) and 48 (−32 [147.1] cells/µL). For the ABC/3TC+3rd agent group, a mean (SD) decrease from baseline was observed at Week 4 (−15 [160.2] cells/µL) before an increase at Week 8 (26 [188.2] cells/µL) through Week 24 (8 [192.9] cells/µL). After switching to GEN for 4 weeks in the Delayed Switch to GEN group, a mean (SD) decrease from baseline was observed (Week 4: −26 [135.7] cells/µL), which was stable through 24 weeks after switching to GEN (Week 24: −23 [201.7] cells/µL) (Table 15.9.2.3).

The percentages of subjects in the FAS with HIV-1 RNA < 20 copies/mL at Weeks 12, 24, and 48, as assessed using the US FDA-defined snapshot algorithm, are presented in Tables 15.9.3.1 through 15.9.3.3. The changes from baseline in CD4% are presented in Table 15.9.3.6.

Of the 274 subjects who received study drug through Week 48, 6 subjects (2.2%) were analyzed for the development of HIV-1 drug resistance (Immediate Switch to GEN group: 4 subjects; Delayed switch to GEN group: 2 subjects). All 6 subjects were receiving GEN at the time of analysis. Of these 6 subjects, 1 subject in the Immediate switch to GEN group developed resistance to study drug (Subject PPD with the reverse transcriptase mutation M184V and the integrase mutation N155H. This subject had suboptimal treatment adherence to study drug (85%) that may have contributed to the development of HIV-1 resistance. None of the 5 other subjects developed resistance, including 3 subjects who achieved HIV-1 RNA resuppression (HIV-1 RNA < 50 copies/mL) after resistance testing was completed.

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

Safety Results: Overall, GEN was generally well tolerated by subjects in the Immediate Switch to GEN and Delayed Switch to GEN groups. The median (Q1, Q3) exposures to study drugs were as follows: Immediate Switch to GEN group: 48.0 (47.6, 48.3) weeks; ABC/3TC+3rd agent group: 24.0 (23.6, 24.1) weeks; Delayed Switch to GEN group: 24.0 (23.9, 24.3) weeks (Table 15.11.1.1).

Adverse Events

Through Week 24, the percentages of subjects who had any AEs whilst receiving study drug were as follows: Immediate Switch to GEN group 65.6% (120 of 183 subjects); ABC/3TC+3rd agent group: 64.8% (59 of 91 subjects). The majority of the AEs were Grade 1 or 2 in severity. The percentages of subjects who had Grade 3 or 4 AEs were as follows: Immediately Switch to GEN group: 4.9% (9 subjects); ABC/3TC+3rd agent group: 0 subject (Table 15.11.2.5.1.1). Two subjects in the Immediate Switch to GEN group had Grade 3 or 4 AEs (hepatocellular injury and hypercholesterolemia) considered related to study drug by the investigator (Table 15.11.2.7.3). Subjects who had any SAEs were as follows: Immediate Switch to GEN group: 2.2% (4 subjects); ABC/3TC+3rd agent group: 1.1% (1 subject). None of the SAEs reported were considered related to study drug by the investigator and none of the SAEs were reported for more than 1 subject. No subjects died through 24 weeks of study. A total of 3.8% (7 subjects) in the Immediate Switch to GEN group had AEs that led to study drug discontinuation. The only AE that led to the discontinuation of study drug that was reported for

more than 1 subject was diarrhea (1.1%, 2 subjects) (Table 15.11.5.2).

The 3 most common AEs reported for subjects through Week 24 were as follows (Table 15.11.2.5.2.2):

- Immediate Switch to GEN group: diarrhea (7.7%; 14 of 183 subjects); headache (7.1%; 13 subjects); and upper respiratory tract infection (6.0%; 11 subjects).
- ABC/3TC+3rd agent group: back pain and vitamin D deficiency (6.6%; 6 of 91 subjects each); and upper respiratory tract infection (5.5%; 5 subjects)

For the Immediate Switch to GEN group, the most common AEs considered related to study drug by investigator through Week 24 were headache (4.4%; 8 of 183 subjects), diarrhea (2.7%; 5 subjects), and asthenia and nausea (2.2%; 4 subjects each). No subjects in the ABC/3TC+3rd agent group had study drug related AEs through Week 24 (Table 15.11.2.7.1.2).

Cumulatively throughout the study (up to Week 48) in the Immediate Switch to GEN group, 79.2% of subjects (145 of 183 subjects) had at least 1 AE. The majority of the AEs were Grade 1 or 2 in severity. A total of 8.2% of subjects (15 subjects) had Grade 3 or 4 AEs (Table 15.11.2.1.1.1). As described above, 2 subjects (1.1%) had Grade 3 or 4 AEs (hepatocellular injury and hypercholesterolemia) considered related to study drug by the investigator (Table 15.11.2.7.3). For the subject who had an AE of hypercholesterolemia, Grade 2 abnormal fasting total cholesterol was reported at baseline (Listing 16.2.8.1.8). A total of 6.6% (12 subjects) of subjects had at least 1 serious AE (SAE) and none were considered related to study drug by the investigator. The only SAE reported for more than 1 subject was pneumonia (0.7%; 2 subjects). No subject died during the study. A total of 4.4% of subjects (8 subjects) had AEs that led to study drug discontinuation.

Cumulatively throughout the study (up to Week 48) in the Immediate Switch to GEN group, the 3 most common AEs reported were diarrhea (10.4%; 19 of 183 subjects), headache (8.2%; 15 subjects), and vitamin D deficiency (7.1%; 13 subjects); and the most common AEs considered related to study drug by the investigator were headache (4.4%; 8 subjects), and asthenia and diarrhea (2.7%; 5 subjects each).

Events that met the Stage 3 opportunistic illness definition of an AIDS-defining diagnosis were reported for 1 subject in the Immediate Switch to GEN group (Kaposi's sarcoma) (Listing 16.2.7.3).

After receiving GEN for 24 weeks in the Delayed Switch to GEN group, 62.9% of subjects (56 of 89 subjects) had at least 1 AE. The majority of AEs were Grade 1 or 2 in severity. A total of 4.5% (4 subjects) had Grade 3 or 4 AEs, and none were considered related to study drug by the investigator. A total of 4.5% of subjects (4 subjects) had at least 1 SAE and none were considered related to study drug by the investigator. No subject died during the study. A total of 1.1% of subjects (1 subject) had an AE that led to study drug discontinuation (pruritus genital).

The 3 most common AEs reported for the Delayed Switch to GEN group were arthralgia (9.0%; 8 of 89 subjects), and diarrhea and headache (4.5%; 4 subjects); and the most common AEs considered related to study drug by the investigator were headache (3.4%; 3 subjects), and abdominal pain and diarrhea (2.2%; 2 subjects each).

The safety results for the All GEN group (subjects who received at least 1 dose of GEN) are consistent with the above and are presented in Tables 15.11.2.1.1.1 through 15.11.2.3.3).

Subject narratives for AEs that led to study drug withdrawal and SAEs are provided in Section 15.2.

Bone Safety

Fracture Events

Overall, trauma-related fractures were reported for 2 of 183 subjects (1.1%) in the Immediate Switch to GEN group. One subject had a foot fracture on Day 14 that was nonserious, Grade 1 in severity, and not considered related to study drug by the investigator. The event resolved and subject continued on study drug. The other subject had humerus fracture on Day 298 that was nonserious, Grade 1 in severity, and not considered related to study drug by the investigator. The event was continuing and subject continued on study drug (Listing 16.2.7.5).

Bone Biomarkers

Through Week 48, similar changes were seen in the median percentage changes from baseline between the Immediate Switch to GEN and ABC/3TC+3rd agent group for PTH and serum OH-25 vitamin D (Tables 15.11.6.6.1 and 15.11.6.6.2).

At Week 24, the median (Q1, Q3) percentage changes from baseline for PTH were as follows: Immediate Switch to GEN group: 0.0% (−19.7%, 27.5%); ABC/3TC+3rd agent group: −2.1% (−19.6%, 29.8%); Delayed Switch to GEN group: −7.3% (−25.8%, 15.3%). At Week 48, the median (Q1, Q3) percentage change from baseline in the Immediate Switch to GEN group was −8.2% (−27.4%, 17.0%).

At Week 24, the median (Q1, Q3) percentage changes from baseline for serum OH-25 vitamin D were as follows: Immediate Switch to GEN group: 0.0% (−26.7%, 32.3%); ABC/3TC+3rd agent group: 4.2% (−20.0%, 32.1%); Delayed Switch to GEN group: 8.2% (−19.3%, 26.4%). At Week 48, the median (Q1, Q3) percentage change from baseline in the Immediate Switch to GEN group was 8.7% (−11.8%, 35.3%).

Renal Safety

Renal Events

Throughout the study, there were no cases of proximal renal tubulopathy reported for any treatment groups whilst receiving study drug, and no subjects discontinued study drug due to a renal AE.

Through Week 24, the renal and urinary disorders or associated investigation AEs reported for subjects in the Immediate Switch to GEN group were as follows: blood creatinine increased (1.1%, 2 of 183 subjects); beta-2-microglobulin increased, chromaturia, leukocyturia, nephrolithiasis, pollakiuria, proteinuria, and renal colic (0.5%; 1 subject each) (Table 15.11.2.5.2.2). These AEs were nonserious. One of the 2 subjects with blood creatinine increased events was considered related to study drug by the investigator (Listing 16.2.7.1). Both AEs of blood creatinine increased were ongoing and the subjects continued with study drug. In the ABC/3TC+3rd agent group, the renal and urinary disorders or associated investigation AEs reported for subjects through Week 24 were as follows: calculus urinary, pollakiuria, and renal colic (1.1%; 1 of 91 subjects each).

Throughout the study (up to Week 48) in the Immediate Switch to GEN group, the cumulative reported renal and urinary disorders or associated investigation AEs were as follows: nephrolithiasis (1.6%, 3 of 183 subjects); blood creatinine increased (1.1%; 2 of 183 subjects); acute kidney injury, beta-2-microglobulin, chromaturia, leukocyturia, pollakiuria, proteinuria, renal colic, and ureterolithiasis (0.5%; 1 subject each) (Table 15.11.2.1.2.1). The AEs of acute kidney injury and ureterolithiasis were serious and were not considered related to study drug by the investigator. The subject with acute kidney injury had a Grade 2 abnormality in serum creatinine and none graded low $eGFR_{CG}$ at baseline (Listing 16.2.8.1.2.2). Both SAEs of acute kidney injury and ureterolithiasis resolved and both subjects continued with study drug (Listing 16.2.7.1). The narratives for these SAEs are provided in Section 15.2.

After receiving GEN for 24 weeks in the Delayed Switch to GEN group, the renal and urinary disorders or associated investigation AEs reported were as follows: renal failure, urethral dilatation, and urinary incontinence (1.1%; 1 of 89 subjects each) (Table 15.11.2.1.2.1). These events were nonserious. The events resolved and were not considered related to the study drug by the investigator. The subjects continued with study drug.

Renal and urinary disorders or associated investigation AEs for the All GEN group are consistent with the above and are presented in Table 15.11.2.1.2.1 through 15.11.2.3.3.

Serum Creatinine and $eGFR_{CG}$

Through Week 24, small and statistically significant differences were observed in the median changes from baseline in serum creatinine and $eGFR_{CG}$ in the Immediate Switch to GEN and ABC/3TC+3rd agent groups. These differences were likely to be driven by whether the baseline ARV regimen taken by subjects contained a creatinine secretion inhibitor. The table below shows the median (Q1, Q3) changes from baseline at Week 24 in serum creatinine of subjects taking a creatinine secretion of inhibitor and subjects not taking a creatinine secretion inhibitor.

	Immediate Switch to GEN		**ABC/3TC+3rd Agent**		**Delay Switch to GEN**		
	n	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**n**	**Median (Q1, Q3)**	**p-value[a]**
Changes from baseline in serum creatinine							
All subjects	171	0.04 (−0.03, 0.13)	89	−0.02 (−0.09, 0.06)	88	0.03 (−0.04, 0.12)	< 0.001
Subjects taking a creatinine secretion inhibitor[b]	85	0.00 (−0.07, 0.06)	47	−0.04 (−0.11, 0.07)	—	—	0.16
Subjects not taking a creatinine secretion inhibitor	86	0.09 (0.02, 0.16)	42	−0.01 (−0.08, 0.06)	—	—	< 0.001

a P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups (Immediate Switch to GEN vs ABC/3TC+3rd Agent).
b A subject was considered to be taking a creatinine secretion inhibitor if their baseline ARV regimen contained a booster (COBI or RTV), DTG or RPV.
Source: Tables 15.11.6.2.8, 15.11.6.2.8.1, and 15.11.6.2.8.2

At Week 48, the median (Q1, Q3) changes from baseline in serum creatinine in the Immediate Switch to GEN group were as follows: all subjects: 0.03 (−0.05, 0.12) mg/dL; subjects taking a creatinine secretion inhibitor: −0.01 (−0.09, 0.05) mg/dL; subjects not taking a creatinine secretion inhibitor: 0.07 (0.01, 0.15) mg/dL (Tables 15.11.6.2.8, 15.11.6.2.8.1, and 15.11.6.2.8.2).

The table below shows the median (Q1, Q3) changes from baseline at Week 24 in $eGFR_{CG}$ of subjects taking a creatinine secretion of inhibitor and subjects not taking a creatinine secretion inhibitor.

	Immediate Switch to GEN		ABC/3TC+3rd Agent		Delay Switch to GEN		
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)	p-value[a]
Changes from baseline in $eGFR_{CG}$							
All subjects	170	−4.8 (−11.4, 4.6)	89	1.8 (−7.8, 8.2)	88	−3.0 (−10.5, 3.9)	0.004
Subjects taking a creatinine secretion inhibitor[b]	84	0.3 (−5.3, 9.0)	47	2.4 (−6.6, 9.0)	—	—	0.95
Subjects not taking a creatinine secretion inhibitor	86	−9.5 (−14.4, −3.0)	42	0.9 (−8.4, 7.8)	—	—	< 0.001

a P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups (Immediate Switch to GEN vs ABC/3TC+3rd Agent).
b A subject was considered to be taking a creatinine secretion inhibitor if their baseline ARV regimen contained a booster (COBI or RTV), DTG or RPV.
Source: Tables 15.11.6.2.9, 15.11.6.2.9.1, and 15.11.6.2.9.2

At Week 48, the median (Q1, Q3) changes from baseline in $eGFR_{CG}$ in the Immediate Switch to GEN group were as follows: all subjects: −3.1 (−10.8, 5.4) mL/min; subjects taking a creatinine secretion inhibitor: 1.2 (−7.2, 9.3) mL/min; subjects not taking a creatinine secretion inhibitor: −8.1 (−15.9, 0.0) mL/min (Tables 15.11.6.2.9, 15.11.6.2.9.1, and 15.11.6.2.9.2).

Proteinuria by Urinalysis (Dipstick)

No subjects had ≥ Grade 3 proteinuria, as assessed by dipstick analysis (Table 15.11.6.4.2). At Week 24, differences in the shift from baseline in graded proteinuria between Immediate Switch to GEN and ABC/3TC+3rd agent group were statistically significant (p = 0.002). Fewer subjects in the Immediate Switch to GEN group compared with the ABC/3TC+3rd agent group had a shift from a < Grade 2 proteinuria at baseline to a Grade 2 proteinuria at Weeks 12 and 24. In the Delayed Switch to GEN group, 1 subject (8.3%) had a switch from < Grade 2 proteinuria at baseline to a Grade 2 after receiving GEN for 24 weeks (Table 15.11.6.8.1).

Proteinuria by Quantitative Assessment

For quantitative measures of albuminuria, UACR decreased from baseline for the Immediate Switch to GEN group and increased for the ABC/3TC+3rd agent group at Week 24 (p = 0.001 for the differences between the 2 groups in median percentage changes from baseline) (Table 15.11.6.8.2.2). The median (Q1, Q3) percentage changes from baseline in UACR at Week 24 were as follows: Immediate Switch to GEN group: −13.3% (−38.2%, 23.4%);

ABC/3TC+3rd agent group: 17.9% (−19.2%, 64.0%); Delayed Switch to GEN group: −5.3% (−33.2%, 32.7%). At Week 48, the median (Q1, Q3) percentage change from baseline in UACR for the Immediate Switch group was −9.3% (−39.3%, 42.7%).

For quantitative measures of UPCR, similar decreases from baseline were seen in both the Immediate Switch to GEN and ABC/3TC+3rd agent group (Table 15.11.6.8.2.1). The median (Q1, Q3) percentage changes from baseline in UPCR at Week 24 were as follows: Immediate Switch to GEN group: −15.7% (−41.4%, 18.6%); ABC/3TC+3rd agent group: −5.8% (−32.8%, 27.9%); Delayed Switch to GEN group: −39.0% (−46.3%, −9.8%). At Week 48, the median (Q1, Q3) percentage change from baseline in UPCR for the Immediate Switch group was −18.9% (−47.8%, 14.2%).

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

For urine RBP to creatinine ratio, decreases from baseline in the Immediate Switch to GEN and increases for the ABC/3TC+3rd agent group were seen at Week 24 (p = 0.068 for the differences between the 2 groups in median percentage changes from baseline) (Table 15.11.6.8.3.1). The median (Q1, Q3) percentage changes from baseline in urine RBP to creatinine ratio at Week 24 were as follows: Immediate Switch to GEN group: −2.4% (−24.8%, 29.6%); ABC/3TC+3rd agent group: 12.3% (−21.1%, 64.6%); Delayed Switch to GEN group: −9.2% (−31.3%, 16.4%). At Week 48, the median (Q1, Q3) percentage change from baseline in urine RBP to creatinine ratio for the Immediate Switch group was 0.2% (−21.2%, 33.3%).

For beta-2-microglobulin to creatinine ratio, decreases from baseline in the Immediate Switch to GEN and increases for the ABC/3TC+3rd agent groups were seen at Week 24 (p = 0.016 for the differences between the 2 groups in median percentage changes from baseline) (Table 15.11.6.8.3.2). The median (Q1, Q3) percentage changes from baseline in urine beta-2-microglobulin to creatinine ratio at Week 24 were as follows: Immediate Switch to GEN group: −9.9% (−47.5%, 33.3%); ABC/3TC+3rd agent group: 3.7% (−27.7%, 67.1%); Delayed Switch to GEN group: −19.5% (−66.7%, 39.6%). At Week 48, the median (Q1, Q3) percentage change from baseline in urine beta-2-microglobulin to creatinine ratio for the Immediate Switch group was −10.7% (−51.3%, 34.0%).

Cardiovascular and Cerebrovascular Safety

Through Week 24, 0.5% (1 of 183 subjects) in the Immediate Switch to GEN group and no subject in the ABC/3TC+3rd agent group had a potential cardiovascular or cerebrovascular event (Table 15.11.2.8.1). The subject in the Immediate Switch to GEN group had a nonserious AE of coronary artery disease, which was not considered related to study drug by the investigator. The AE was ongoing and the subject continued with study drug (Listing 16.2.7.4).

Cumulatively throughout the study (up to Week 48) in the Immediate GEN group, 1.6% of subjects (3 of 183 subjects) had a potential cardiovascular or cerebrovascular event, which were coronary artery disease (1.1%; 2 subjects) and myocardial infarction (0.5%; 1 subject) (Table 15.11.2.4.1). Serious AEs were reported for 1 of the coronary artery disease events and the myocardial infarction event (Table 15.11.4.1). All of the potential cardiovascular or cerebrovascular events were not considered related to study drug by the investigator, and all subjects continued with their study drug (Listing 16.2.7.4).

After receiving GEN for 24 weeks in the Delayed Switch to GEN group, no subjects had a cardiovascular or cerebrovascular event (Table 15.11.2.4.1).

The cardiovascular and cerebrovascular safety results for the All GEN group are consistent with the above and are presented in Table 15.11.2.4.1.

Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for hematology and clinical chemistry in any treatment group at both Weeks 24 and 48, and the median values were within the normal ranges.

Through Week 24, the majority of the subjects in both the Immediate Switch to GEN and ABC/3TC+3rd agent groups had at least 1 laboratory abnormality reported (Immediate Switch to GEN group: 76.9%, 140 of 182 subjects; ABC/3TC+3rd agent group: 73.3%, 66 of 90 subjects) (Table 15.11.6.4.3). Most of the reported abnormalities were Grade 1 or 2. The percentages of subjects with Grade 3 or 4 laboratory abnormalities through Week 24 were as follows: Immediate Switch to GEN group: 13.2% (24 subjects); ABC/3TC+3rd agent group: 8.9% (8 subjects). The most commonly reported Grade 3 or 4 laboratory abnormality was fasting LDL cholesterol increased for both the Immediate Switch to GEN group (8.0%, 14 subjects) and ABC/3TC+3rd agent group (5.6%, 5 subjects). A total of 4 subjects had a Grade 4 laboratory abnormality (Immediate Switch to GEN group: 1.1%, 2 subjects; ABC/3TC+3rd agent group: 2.2%, 2 subjects) (Table 15.11.6.4.4). The Grade 4 laboratory abnormalities reported in the Immediate Switch to GEN group were as follows: ALT increased and neutrophils decreased (0.5%, 1 subject each). The Grade 4 laboratory abnormalities reported in the ABC/3TC+3rd agent group were as follows: ALT increased and fasting triglycerides increased (1.1%, 1 subject each).

Cumulatively throughout the study (up to Week 48) in the Immediate Switch to GEN group, 84.1% of subjects (153 of 183 subjects) had at least 1 laboratory abnormality reported (Table 15.11.6.4.1). Most of the reported abnormalities were Grade 1 or 2. A total of 17.0% of subjects (31 of 182 subjects) had at least 1 Grade 3 or 4 laboratory abnormalities. The most commonly reported Grade 3 or 4 laboratory abnormality was fasting LDL cholesterol increased (9.7%; 17 of 176 subjects) (Table 15.11.6.4.2). Grade 4 laboratory abnormalities were reported for 2.7% of subjects (5 of 182 subjects) and were as follows: increased alanine transaminase (ALT) (1.1%; 2 of 182 subjects); decreased neutrophils (0.5%; 1 of 182 subjects); hyperglycemia (0.5%; 1 of 182 subjects); and fasting triglycerides increased (0.6%; 1 of 176 subjects).

After receiving GEN for 24 weeks in the Delayed Switch to GEN group, 71.9% of subjects (64 of 89 subjects) had at least 1 laboratory abnormality reported (Table 15.11.6.4.1). Most of the reported abnormalities were Grade 1 or 2. A total of 9.0% of subjects (8 of 89 subjects) reported at least 1 Grade 3 laboratory abnormality and no subjects had a Grade 4 laboratory abnormality. The most commonly reported Grade 3 laboratory abnormality was fasting LDL cholesterol increased (5.7%; 5 of 88 subjects).

The laboratory abnormalities results for the All GEN group are consistent with the above and are presented in Tables 15.11.6.4.1 and 15.11.6.4.2.

Metabolic Laboratory Parameters

Through Week 24, the changes in the median values in lipid parameters were generally similar and not clinically relevant for both the Immediate Switch to GEN and ABC/3TC+3rd agent groups. Of the lipid parameters, fasting total cholesterol increased from baseline for the Immediate Switch to GEN group and no change from baseline was seen in the ABC/3TC+3rd agent group at Week 24 ($p = 0.020$ for the differences between the 2 groups in median changes from baseline) (Table 15.11.6.3.1). However, for subjects who were not taking lipid-modifying medications either at study entry or during the study, fasting total cholesterol increased in both the Immediate Switch to GEN and ABC/3TC+3rd agent group at Week 24 ($p = 0.087$ for the differences between the 2 groups in median changes from baseline) (Table 15.11.6.3.9). At Week 48, the changes from baseline in the fasting lipid parameters and glucose were similar to Week 24 for the Immediate Switch to GEN group.

Through Week 24, the majority of graded hypercholesterolemia and fasting LDL were Grade 1 or 2 for both the Immediate Switch to GEN and ABC/3TC+3rd agent groups (Table 15.11.6.4.3). No Grade 4 abnormal lipid parameters were reported for the Immediate Switch to GEN group and Grade 4 fasting triglycerides increased was reported for 1 of 91 subjects (1.1%) in the ABC/3TC+3rd agent group. The percentages of subjects who had Grade 3 abnormal parameters were as follows (Table 15.11.6.4.4):

- Fasting hypercholesterolemia: Immediate Switch to GEN group: 5.1% (9 of 176 subjects); ABC/3TC+3rd agent group: 1.1% (1 of 90 subject)
- Fasting triglycerides increased: Immediate Switch to GEN group: 1.1% (2 of 176 subjects); ABC/3TC+3rd agent group: 1.1% (1 of 90 subjects)
- Fasting LDL increased: Immediate Switch to GEN group: 8.0% (14 of 176 subjects); ABC/3TC+3rd agent group: 5.6% (5 of 90 subjects)

Cumulatively throughout the study (up to Week 48) in the Immediate Switch to GEN group, the majority of fasting hypercholesterolemia and fasting LDL increased were Grade 1 or 2 (Table 15.11.6.4.1). Grade 4 fasting triglycerides increased was reported for 0.6% of subjects (1 of 176 subjects) and Grade 4 fasting hyperglycemia was reported for 0.5% of subjects (1 of 182 subjects). Grade 3 abnormal lipid parameters reported were as follows: fasting LDL increased (9.7%; 17 of 176 subjects), fasting hypercholesterolemia (6.8%; 12 of 176 subjects), and fasting triglycerides increased (1.1%; 2 of 176 subjects) (Table 15.11.6.4.2).

After receiving GEN for 24 weeks in the Delayed Switch to GEN group, the majority of fasting hypercholesterolemia, fasting triglycerides increased, fasting LDL increased, and all fasting hyperglycemia and fasting hypoglycemia were Grade 1 or 2 (Table 15.11.6.4.1). No Grade 4 abnormal fasting lipid parameters were reported. Grade 3 abnormal lipid parameters reported were as follows: fasting hypercholesterolemia (3.4%; 3 of 88 subjects) and fasting LDL increased (5.7%; 5 of 88 subjects) (Table 15.11.6.4.2).

The abnormal lipid parameters for the All GEN group were consistent with the above and are presented in Tables 15.11.6.4.1 and 15.11.6.4.2.

Patient Reported Outcomes Results:

Through Week 24, subjects in the Immediate Switch to GEN group reported significant improvement in treatment satisfaction compared with those who remained on ABC/3TC+3rd agent ($p < 0.001$) (Table 15.12.3). There were no differences between treatment groups for other PROs including adherence, VAS, EQ-5D-3L, SF-36, and FACIT-F (Tables 15.12.1.1, 15.12.2, 15.12.4 through 15.12.5.4). At Week 48, similar PROs results to Week 24 were reported for the Immediate Switch to GEN group.

CONCLUSIONS:

The conclusions from this study are as follows:

- In the Immediate Switch to GEN group, high rates of virologic suppression were maintained over 48 weeks of treatment and GEN was noninferior to ABC/3TC+3rd agent using the protocol-specified 12% noninferiority margin at Week 24.
- After switching to GEN for the Delayed Switch to GEN group, the safety and efficacy results were consistent with the Immediate Switch to GEN group.
- Virologic resistance to study drug was noted in 1 subject with suboptimal adherence at Week 12 in the Immediate Switch to GEN group.
- GEN was well tolerated as demonstrated by the low incidence of SAEs and AEs leading to discontinuation of study drug. None of the reported SAEs were study drug related. Adverse events reported were consistent with the safety profile of GEN.
- No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported after subjects had switched to GEN and none of the renal and urinary disorder or associated investigation AEs led to discontinuation of study drug.
- Changes in serum creatinine and $eGFR_{CG}$ were observed after switching to GEN; however, these changes were likely to be driven by whether the baseline ARV regimen taken by subjects contained a creatinine secretion inhibitor.
- Decreases from baseline in renal biomarkers (proteinuria by quantitative assessments, urine RBP to creatinine ratio, and beta-2-microglobulin to creatinine ratio) were seen after switching to GEN.
- Changes seen in fasting lipid parameters and total cholesterol to HDL ratio were not clinically significant after switching to GEN.