FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1 Infected Virologically Suppressed Adolescents
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-292-1515
Phase of Development:	Phase 2/3
IND No.: **EudraCT No.:**	111,007 2014-002673-11
ClinicalTrials.gov Identifier:	NCT02276612
Study Start Date:	03 December 2014 (First Subject Screened)
Study End Date:	10 November 2016 (Last Subject Last Observation for the Primary Endpoint)
Principal or Coordinating Investigator:	Name: Avy Violari, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Cheryl Pikora, MD PhD Telephone: PPD Fax: PPD
Report Date:	26 March 2018

STUDY SYNOPSIS
Study GS-US-292-1515

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

Title of Study: A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1 Infected Virologically Suppressed Adolescents

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled into a total of 9 study centers: 4 in the United States (US) and 5 in South Africa.

Publications: There were no publications at the time of this CSR.

Study Period:

03 December 2014 (First Subject Screened)
10 November 2016 (Last Subject Last Observation for the Primary Endpoint)
23 October 2017 (Global Last Subject Last Visit)

Phase of Development: Phase 2/3

Objectives:

The primary objective of this study was as follows:

- To evaluate the safety and tolerability of elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (E/C/F/TAF; Genvoya®; GEN) in HIV-infected virologically suppressed adolescents 12 to < 18 years of age.

The secondary objective of this study was as follows:

- To evaluate the efficacy (antiviral activity) of switching to GEN in HIV-infected virologically suppressed adolescents 12 to < 18 years of age.

This report describes results for the adolescent subjects, the results for the 10 subjects aged ≥ 18 years are presented in the preprogrammed tables, figures, and listings.

Methodology: This was an open-label, single-arm study to evaluate the safety, efficacy, and tolerability of switching to GEN in adolescents (ages 12 to <18 years) who were virologically suppressed (HIV-1 RNA < 50 copies/mL for ≥ 6 months) on their current stable antiretroviral (ARV) regimen. A total of approximately 50 subjects of either sex were to be enrolled.
All subjects switched their treatment to GEN at baseline/Day 1.

Subjects returned for study visits at baseline/Day 1, Weeks 1, 2, 4, 8, 12, 24, and 48. Height and weight were measured at every visit. Tanner stage and dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine and total body were performed at baseline/Day 1, Weeks 24, and 48. Serum was collected for bone biomarkers (collected fasted) including bicarbonate, N-telopeptide, C-telopeptide, osteocalcin, bone specific alkaline phosphatase, procollagen type 1 N-terminal propeptide, C-type collagen sequence, and parathyroid hormone, 1,25-OH vitamin D and 25-OH vitamin D, and urine bicarbonate and N-telopeptide at baseline/Day 1, Weeks 4, 12, 24, and 48.

Urine was collected for urinalysis and urine chemistry at every visit. Selected renal biomarkers including, urine chemistry, retinol binding protein (RBP), and beta-2-microglobulin were collected at baseline/Day 1, Weeks 4, 12, 24, and 48, with subjects in a fasted state.

Metabolic assessments including fasting glucose and lipid panel (total cholesterol, high density lipoprotein, direct low-density lipoprotein [LDL], and triglycerides) were collected at baseline/Day 1, Weeks 24, and 48 for subjects who were able to fast.

Clinical chemistry and hematology assessments, including platelet counts were collected at all study visits.

Subjects who completed the study through Week 48 were given the option to participate in an extension phase of the study.

Subjects who completed through Week 48 but did not participate in the extension phase, as well as subjects who prematurely discontinued prior to Week 48, were required to return to the clinic 30 days after the last dose of the study drug for a 30-Day Follow-up visit.

In the extension phase of the study, subjects returned for study visits every 12 weeks for review of adverse events (AEs) and concomitant medications, physical exams, vital signs, weight/height measurements, urine collection, blood sampling, estimated glomerular filtration rate (eGFR), CD4 cell count and percentage, plasma HIV-1 RNA, study drug dispensation and accountability. In addition to the above, metabolic assessments, Tanner Stage assessments, and DXA scans were performed every 48 weeks, and bone biomarkers were collected every 24 weeks.

Following participation in the extension phase of the study, subjects with virologic suppression (HIV-1 RNA < 50 copies/mL) were given the option of rolling over and screen for eligibility to participate in another Gilead study (GS-US-380-1474).

Number of Subjects (Planned and Analyzed):
Planned: 50 subjects
Analyzed (by analysis set):

Analysis Set	GEN
Subjects Enrolled	50
Subjects in Safety Analysis Set	50 (100.0%)
Subjects in Full Analysis Set (FAS)	50 (100.0%)
Subjects in PK Analysis Set	50 (100.0%)
Subjects in Spine BMD Analysis Set	50 (100.0%)
Subjects in Total Body Less Head (TBLH) BMD Analysis Set	49 (98.0%)

Diagnosis and Main Criteria for Inclusion: HIV-1 infected adolescents (12 to < 18 years), weighed ≥ 35 kg, were on a stable ARV regimen for ≥ 6 consecutive months prior to screening and had CD4 cell count > 100 cells/μL.

Plasma HIV-1 RNA levels must have been < 50 copies/mL for ≥ 6 consecutive months prior to baseline/Day 1 and had not experienced 2 consecutive HIV-1 RNA above detectable levels after achieving a confirmed (2 consecutive) HIV-1 RNA below detectable levels on the current regimen in the past year.

Subjects had to have eGFR ≥ 90 mL/min/1.73 m^2 by pediatric (Schwartz) formula, no evidence of HBV or HCV infection, and no documented history of resistance to EVG, FTC, lamivudine (3TC), or tenofovir (TFV), including but not limited to: the presence of reverse transcriptase (RT) mutations K65R, K70E, M184V/I, or 3 or more thymidine analog-associated mutations (TAMs) that included M41L or L210W (TAMs were M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R).

Duration of Treatment: Subjects received open-label GEN for 48 weeks.

After completion of 48 weeks, all eligible subjects were given the option to participate in an extension phase of the study until:

- The subject turned 18 years old and GEN was commercially available for the use in adults in the country in which the subject was enrolled, or
- GEN became commercially available for use in the subject's current age group in the country in which the subject was enrolled, or
- GEN became accessible to subjects through an access program, or
- Gilead elected to terminate development of GEN in the applicable country

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

Batch Numbers: CP1315B1, CP1401B1, CP1403B1, CP1501B1, CP1506B1, CP1603B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: None.

Criteria for Evaluation:

Efficacy: The efficacy endpoints were as follows:

- Percentage of subjects with HIV-1 RNA < 50 copies/mL (as defined by the US Food and Drug Administration [FDA]-defined snapshot algorithm) at Weeks 24 and 48
- Change from baseline in CD4 cell count and CD4 percentage at Weeks 24 and 48
- The percentages of subjects with HIV-1 RNA < 50 copies/mL by missing = failure (M = F) and missing = excluded (M = E) analyses at Weeks 24 and 48

Pharmacokinetics: Single and trough pharmacokinetic (PK) samples were collected on or between the Weeks 2 and 4 visits and once on or between the Weeks 8 and 12 visits.

Safety: Safety assessments included incidence of treatment emergent serious AEs (SAEs) and AEs, clinical laboratory tests, selected renal and bone biomarkers, and bone mineral density (BMD; assessed by DXA).

Statistical Methods:

Efficacy:

Analyses of efficacy endpoints used the Full Analysis Set (FAS). The FAS included all subjects who were enrolled in the study and had received ≥ 1 dose of study drug. The numbers and percentages of subjects with HIV-1 RNA < 50 copies/mL were summarized based on the US FDA-defined snapshot algorithm, M = F and M = E analyses. The 95% CI for the percentage estimate was constructed using the Clopper-Pearson Exact method. For the US FDA-defined snapshot algorithm, the numbers and percentages of subjects with HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL (including subcategories), and no virological data (including reasons) were summarized. For the M = F analysis, results were summarized for all visits up to Week 48. For the M = E analysis, results were summarized at all visits for the FAS. The CD4 cell count and CD4% data were summarized using observed, on treatment data (ie, up to 1 day after the last dose date of study drug).

Pharmacokinetics:

The PK analyses were conducted using the PK Analysis Set for the single PK sampling and trough PK sampling that occurred on or between the Week 2 and 4 visits, and on or between the Week 8 and 12 visits. The PK Analysis Set included all subjects who were enrolled and received at least 1 dose of study drug and for whom concentration data for any analytes of interest were available.

Safety:

The Safety Analysis Set included all subjects who were enrolled in the study and had received ≥ 1 dose of study drug. All safety data collected were summarized using descriptive statistics. For subjects who permanently discontinued study drug, all safety data collected from the first dose date to up to 30 days after the last dose date were included. All safety data collected were listed for all enrolled subjects.

The Spine and TBLH BMD Analysis Sets included all subjects who were enrolled in the study, had received ≥ 1 dose of study drug, and had a nonmissing baseline and ≥ 1 postbaseline spine or TBLH BMD value, respectively. Percentage changes from baseline in BMD and changes from baseline in standard and height-age BMD Z-scores were summarized using descriptive statistics.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 56 screened subjects, 50 were enrolled into the study and received at least 1 dose of GEN.

In the Safety Analysis Set, 64.0% were female. The median age of subjects was 15 years (range: 13 to 16 years). Most of the subjects were black (98.0%), and not Hispanic/Latino (98.0%).

The median (Q1, Q3) body weight of subjects at baseline was 52.2 (44.4, 61.3) kg; and the median (Q1, Q3) baseline Z-score for weight was −0.36 (−1.15, 0.36). The median (Q1, Q3) baseline height was 158.9 (152.0, 165.7) cm; and the median (Q1, Q3) baseline Z-score for height was −0.62 (−1.39, 0.19). The median (Q1, Q3) value for body mass index at baseline was 19.8 (17.9, 22.6) kg/m2, and the median (Q1, Q3) baseline eGFR calculated using the Schwartz and modified Schwartz formulae were 157.5 (140.5, 175.7) mL/min/1.73 m2 and 117.2 (109.7, 125.7) mL/min/1.73 m2, respectively. Pubertal stage at baseline varied widely among study subjects. For males, pubertal stage at baseline was Tanner stages 1-3 for 9 subjects (50.0%) and stages 4-5 for 9 subjects (50.0%). For females, pubertal stage at baseline was Tanner stages 1-3 for 8 subjects (25.0%) and stages 4-5 for 24 subjects (75.0%).

Forty-nine (98.0%) subjects had plasma HIV-1 RNA < 50 copies/mL at baseline. Median (Q1, Q3) baseline CD4 cell count was 742 (598, 942) cells/μL; 90.0% of subjects had CD4 cell counts ≥ 500 cells/μL. The median (Q1, Q3) CD4% was 34.3% (30.1, 38.6). The median (Q1, Q3) number of years since diagnosis of HIV infection was 12.0 years (9.0, 14.0). The most common HIV risk factor was vertical transmission (80.0%). The majority of subjects had asymptomatic HIV-1 infection; 12 subjects (24.0%) had symptomatic HIV-1 infection and 1 subject (2.0%) was diagnosed with AIDS. No subject was hepatitis B surface antigen or HCV antibody positive.

All subjects were receiving at least 1 ARV drug in accordance with study entry criteria. Thirty -eight of 50 subjects (76.0%) were receiving a nucleoside reverse transcriptase inhibitor (NRTI), and the most common NRTI taken was abacavir (36.0%). Twenty-one subjects (42.0%) were receiving protease inhibitors, and the most common protease inhibitor taken was lopinavir/ritonavir (36.0%). Seventeen subjects (34.0%) were receiving a nonnucleoside reverse transcriptase inhibitor (NNRTI), and the most common NNRTI taken was efavirenz (EFV; 32.0%). Twelve subjects (24.0%) were receiving a single tablet regimen, and the most common single tablet regimen taken was Atripla® (EFV/FTC/tenofovir disoproxil fumarate; 18.0%).

Efficacy Results:

At Weeks 24 and 48, 96.0% and 90.0% of subjects in the FAS had HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm), respectively. At Week 24, 2 subjects had HIV-1 RNA ≥ 50 copies/mL. One subject remained on study drug and had HIV-1 RNA < 50 copies/mL at Week 48. The other subject continued with study drug and had HIV-1 RNA ≥ 50 copies/mL at Week 48. At Week 48, 4 subjects had HIV-1 RNA ≥ 50 copies/mL. All but 1 of these subjects had HIV-1 RNA < 50 copies/mL prior to the Week 48 analysis window. The subject who had HIV-1 RNA ≥ 50 copies/mL at both Weeks 24 and 48 subsequently discontinued study drug due to physician's decision. The physician's decision to discontinue study drug was due to the subject having compliance issues that led to elevated viral loads without any resistance detected.

Mean (SD) changes from baseline (753 [222.5] cells/μL) in the CD4 cell count were as follows: Week 24: −72 (189.8) cells/μL; Week 48: −43 (201.1) cells/μL. The mean (SD) changes from baseline in CD4% were as follows: Week 24: −0.6% (5.46%); Week 48: −0.1% (3.95%).

Through to the end of GEN treatment, 5 of 50 subjects (10%) were analyzed for resistance. Two subjects had the secondary integrase mutation M50I detected, with no phenotypic resistance seen. The remaining 3 subjects had no resistance to any study drug. Overall, no phenotypic and genotypic resistance to GEN developed through the end of this study.

Safety Results: GEN was well tolerated by the 50 HIV-infected, virologically suppressed adolescent subjects aged 12 to < 18 years through a median duration of exposure of 111.6 weeks. Overall, all subjects in the Safety Analysis Set received GEN for ≥ 24 weeks and 96.0% of subjects received GEN for ≥ 48 weeks.

Adverse Events

Overall, most subjects (94.0%; 47 of 50 subjects) had at least 1 AE. The 3 most commonly reported AEs were cough (24.0%; 12 subjects); upper respiratory tract infection (22.0%; 11 subjects); and vomiting (18.0%, 9 subjects). At Week 24, the 3 most common reported AEs were cough (18.0%, 9 subjects); and diarrhea and vomiting (14.0%, 7 subjects each). At Week 48, the 3 most commonly reported AEs were cough (20.0%, 10 subjects); vomiting and upper respiratory tract infection (16.0%, 8 subjects each).

The majority of the AEs were Grade 1 or 2 in severity; Grade 3 or 4 AEs were reported for 5 subjects (10.0%), of which 1 subject died (Grade 4 electrocution). None of these Grade 3 or 4 AEs were study drug related and none had led to discontinuation of study drug. Study drug related AEs that occurred in > 1 subject were rash (6.0%, 3 subjects), and vomiting and bone density decreased (4.0%, 2 subjects each).

One treatment-emergent death was reported during the study (electrocution), which was not related to study drug. Two subjects had SAEs during the study (Weeks 24 and 48: 1 subject each). Of these, 1 subject had a Grade 2 SAE of vomiting that was considered related to study drug through Week 24, and the other subject had a spontaneous abortion through Week 48. Two subjects discontinued study drug due to an AE. One subject had a Grade 1 iridocyclitis that was considered related to study drug, and 1 subject had a Grade 1 pulmonary tuberculosis, which was considered a Centers for Disease Control and Prevention (CDC) Class C AIDS defining event and not related to study drug. Both AEs of iridocyclitis and pulmonary tuberculosis

resolved after the subjects discontinued study drug and received non-ARV concomitant treatments.

Five confirmed pregnancies were reported during the study. Two pregnancies resulted in spontaneous abortion, 1 resulted in delivery of a healthy baby boy with no complications, 1 pregnancy was ongoing, and 1 pregnancy underwent a nontherapeutic termination.

Bone Safety

One subject had a nonserious, Grade 1 foot fracture. The fracture was considered not related to study drug and the subject continued with the study drug.

Mean (SD) and median (Q1, Q3) baseline values and percentage changes from baseline at Weeks 24 and 48 in spine and TBLH BMD are shown in the table below.

	Spine BMD (N = 50)[a]			TBLH BMD (N =49)[b]		
Time Point	**n**	**Mean (SD)**	**Median (Q1, Q3)**	**n**	**Mean (SD)**	**Median (Q1, Q3)**
Baseline (g/cm^2)	50	0.835 (0.1644)	0.817 (0.740, 0.959)	49	0.838 (0.1051)	0.821 (0.763, 0.898)
% Change at Week 24	49	3.584 (3.5648)	2.742 (1.005, 6.359)	48	1.378 (2.2709)	1.188 (−0.058, 3.164)
% Change at Week 48	49	5.446 (5.9703)	3.594 (1.638, 7.475)	47	3.013 (3.0282)	2.758 (0.308, 5.234)

a Only subjects with nonmissing baseline spine BMD were included in Spine BMD Analysis Set.
b Only subjects with nonmissing baseline TBLH BMD were included in TBLH BMD Analysis Set.
% Chg = Change from baseline at a postbaseline visit/baseline * 100%.

At Week 24, no subjects had a ≥ 4% decrease from baseline in spine or TBLH BMD. At Week 48, 1 of 49 subjects had a ≥ 4% decrease from baseline in spine BMD and no subjects had a ≥ 4% decrease from baseline in TBLH BMD. The subject who had ≥ 4% decrease had an increase in the percentage change from baseline in spine BMD at subsequent visits, ranging from 3.853% (Week 72) to 16.248% (Week 120). This subject did not have a ≥ 4% decrease in spine BMD at any other visit or any AEs related to bone mineral decreased at any time during the study.

Baseline spine standard and height age BMD Z-scores, and changes from baseline in each at Weeks 24 and 48, are shown in the table below.

	Spine BMD Z-Score (Standard) (N = 50)[a]			Spine BMD Z-Score (Height-Age) (N =50)[a, b]		
Time Point	**n**	**Mean (SD)**	**Median (Q1, Q3)**	**n**	**Mean (SD)**	**Median (Q1, Q3)**
Baseline	50	−0.98 (1.156)	−0.91 (−1.87, −0.21)	39	0.03 (1.363)	−0.14 (−0.81, 0.70)
Change at Week 24	49	0.08 (0.250)	0.11 (−0.14, 0.23)	36	0.07 (0.356)	0.14 (−0.13, 0.29)
Change at Week 48	49	0.03 (0.370)	0.07 (−0.20, 0.20)	36	0.03 (0.481)	0.05 (−0.20, 0.36)

a Only subjects with nonmissing baseline spine BMD were included in Spine BMD Analysis Set.
b Some subjects had missing height-age Z-scores because their height-ages were outside the BMD reference data for Z-scores.

Baseline TBLH standard and height-age BMD Z-scores, and changes from baseline in each at Weeks 24 and 48, are shown in the table below.

Time Point	TBLH BMD Z-Score (Standard) (N = 49)[a]			TBLH BMD Z-Score (Height-Age) (N = 49)[a, b]		
	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)
Baseline	49	−1.41 (1.100)	−1.63 (−2.06, −0.76)	39	−0.45 (1.333)	−0.61 (−1.37, 0.46)
Change at Week 24	48	−0.01 (0.224)	0.00 (−0.18, 0.16)	36	−0.05 (0.470)	−0.03 (−0.25, 0.22)
Change at Week 48	47	0.02 (0.255)	0.06 (−0.16, 0.21)	35	−0.02 (0.508)	0.09 (−0.24, 0.28)

a Only subjects with nonmissing baseline TBLH BMD were included in TBLH BMD Analysis Set.
b Some subjects had missing height-age Z-scores because their height-ages were outside the BMD reference data for Z-scores

Two subjects (4.0%) had AEs related to BMD (ie, bone density decreased). Both AEs of bone density decreased were nonserious and were considered related to study drug. Both subjects continued study drug.

There were no changes from baseline in spine or TBLH height-age clinical status (a change from a baseline Z-score of > −2 to ≤ −2) that were considered to be indicative of possible significant bone loss at either Week 24 or 48.

Renal Safety

No subject had proximal tubulopathy (including Fanconi syndrome) or discontinued study drug due to a renal and urinary disorder or associated investigation AEs.

Median (Q1, Q3) baseline serum creatinine was 0.60 (0.53, 0.68) mg/dL. Increases from baseline were observed from Week 1 through Week 48. Median (Q1, Q3) changes from baseline were as follows: Week 1: 0.02 (−0.04, 0.06) mg/dL; Week 24: 0.08 (0.02, 0.14) mg/dL; Week 48: 0.11 (0.03, 0.16) mg/dL. No graded serum creatinine abnormalities were reported.

Median (Q1, Q3) baseline eGFR using the Schwartz formula was 157.5 (140.5, 175.7) mL/min/1.73 m2. Corresponding to the increase in serum creatinine, decreases in eGFR using the Schwartz formula were observed from Week 1 through Week 48. Median (Q1, Q3) changes from baseline were as follows: Week 1: −3.0 (−13.2, 9.9) mL/min/1.73 m2; Week 24: −14.8 (−28.4, −4.7) mL/min/1.73 m2; Week 48: −19.4 (−32.1, −4.4) mL/min/1.73 m2.

Median (Q1, Q3) baseline eGFR using the modified Schwartz formula was 117.2 (109.7, 125.7) mL/min/1.73 m2. Decreases were observed from Week 2 through Week 48. Median (Q1, Q3) changes from baseline were as follows: Week 2: −5.1 (−11.5, 0.1) mL/min/1.73 m2; Week 24:−10.8 (−15.5, −1.1) mL/min/1.73 m2; Week 48: −7.0 (−17.0, −1.8) mL/min/1.73 m2.

Median (Q1, Q3) baseline cystatin C was 0.60 (0.53, 0.64) mg/L. Median (Q1, Q3) changes from baseline were as follows: Week 24: 0.04 (−0.01, 0.07) mg/mL; Week 48: 0.00 (−0.03, 0.07) mg/L.

Median serum phosphorus values were within normal ranges throughout the study. Grade 1 hypophosphatemia was reported for 2 subjects (4.0%) and Grade 3 hypophosphatemia was reported for 1 subject (2.0%).

At baseline, 2 subjects (4.0%) had Grade 1 proteinuria, as assessed by dipstick analysis. Treatment-emergent Grade 1 or 2 proteinuria was reported for 15 subjects (30.0%; Grade 1: 13 subjects [26.0%]; Grade 2: 2 subjects [4.0%]) and was generally isolated and transient.

The changes from baseline fluctuated throughout the study in specific markers of proximal tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio). Median (Q1, Q3) percentage changes from baseline at Weeks 24 and 48 were as follows:

- Urine RBP to creatinine ratio: Week 24: −15.1 % (−35.5%, 35.4%); Week 48: 2.4 % (−41.3%, 36.4%)
- Urine beta-2-microglobulin to creatinine ratio: Week 24: −13.2% (−52.2%, 0.7%); Week 48: −10.6% (−29.7%, 26.1%).

Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for both hematology (including platelet counts) and clinical chemistry parameters. Generally, median values were within normal ranges. Most subjects had at least 1 laboratory abnormality reported during the study (98.0%, 49 of 50 subjects). Grade 3 or 4 laboratory abnormalities were reported for 18 subjects (36.0%; Grade 3: 34.0%, 17 subjects; Grade 4: 2.0%, 1 subject). The most common Grade 3 or 4 laboratory abnormalities were quantitative hematuria (18.2%, 8 of 44 subjects) and decreased neutrophils (16.0%, 8 of 50 subjects). All 8 subjects who had Grade 3 or 4 quantitative hematuria were females, and all had confirmed menses as etiology apart from 1 subject. The Grade 3 or 4 quantitative hematuria for this subject was related to a miscarriage. Of the 8 subjects who had Grade 3 or 4 decreased neutrophils, there was one Grade 4 abnormality of decreased neutrophils reported at Week 4. This subject had low neutrophil counts from baseline (Grade 3 on Day 1) and throughout the study. No subject met Hy's law criteria.

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline in median values for metabolic laboratory parameters. Graded abnormalities in fasting glucose and the majority of lipid parameters were infrequent, and were mostly Grade 1 or 2. Two subjects (4.0%) had a Grade 3 LDL cholesterol increase, both subjects had a Grade 1 or 2 LDL cholesterol increase at baseline.

Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no clinically relevant changes in any vital signs parameter in any subject during the study. Changes in Tanner stage were consistent with the maturing population.

CONCLUSIONS:

The conclusions for HIV-infected, virologically suppressed adolescent subjects treated with GEN in this study are as follows:

- At Weeks 24 and 48, 96.0% and 90.0% of subjects in the FAS had HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm), respectively; thus, virologic suppression was maintained for adolescent subjects switching to GEN (E/C/F/TAF 150/150/200/10 mg) treatment.
- Changes in CD4 cell count were minimal through Week 48, and there was little change in CD4% throughout the study. As such, these changes were not considered clinically relevant.
- GEN was well tolerated, as demonstrated by the low incidence of SAEs and AEs leading to study drug discontinuation.
- Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine in adults, and are not considered reflective of changes in actual glomerular filtration.
- The lack of notable changes from baseline in height-age spine and TBLH BMD Z-scores at Weeks 24 and 48 indicates that subjects mineralized bone at rates consistent with those of the reference population.