# FINAL SYNOPTIC CLINICAL STUDY REPORT

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| **Study Title:** | A Phase 3b Open-label Study of the Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1/Hepatitis B Co-infected Adults |
| **Name of Test Drug:** | Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF [E/C/F/TAF] Genvoya® [GEN]) |
| **Dose and Formulation:** | Fixed-dose combination tablet of E/C/F/TAF (150/150/200/10 mg) |
| **Indication:** | HIV-1 and hepatitis B coinfection |
| **Sponsor:** | Gilead Sciences, Inc<br>333 Lakeside Drive<br>Foster City, CA 94404<br>USA |
| **Study No.:** | GS-US-292-1249 |
| **Phase of Development:** | Phase 3b |
| **IND No.:** | 111007 |
| **EudraCT No.:** | Not Applicable |
| **ClinicalTrials.gov Identifier:** | NCT 02071082 |
| **Study Start Date:** | 25 February 2014 (First Subject Screened) |
| **Study End Date:** | 26 October 2016 (Last Subject Last Observation for this Report |
| **Principal or Coordinating Investigator:** | Name: Joel Gallant, MD, MPH<br>Affiliation: PPD |
| **Gilead Responsible Medical Monitor:** | Name: Moupali Das, MD<br>Telephone: PPD<br>Fax: PPD |
| **Report Date:** | 13 April 2017 |
| **Previous Report Date(s):** | 28 August 2015 (Interim Week 48) |

# STUDY SYNOPSIS

## Study GS-US-292-1249

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

**Title of Study:** A Phase 3b Open-label Study of the Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1/Hepatitis B Co-infected Adults

**Investigators:** Multicenter

**Study Centers:** This was a multicenter study with 21 centers in the United States (US), 2 centers in Canada, and 1 center in Japan.

**Publications:** Gallant J, Brunetta J, Crofoot G, et al. Brief Report: Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1/Hepatitis B Coinfected Adults. J Acquir Immune Defic Syndr 2016;73 (3):294-98.

**Study Period:**

25 February 2014 (First Subject Screened)
26 October 2016 (Last Subject Last Observation for this Report)

**Phase of Development**: Phase 3b

**Objectives:**

The objectives of this study were as follows:

- To characterize the anti-hepatitis B virus (HBV) efficacy profile of a single-tablet regimen (also referred to as a fixed-dose combination [FDC]) consisting of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF; [E/C/F/TAF]; Genvoya® [GEN]) in HIV/HBV coinfected subjects as determined by the proportion of subjects with plasma HBV DNA below 29 IU/mL at Weeks 24 and 48
- To characterize the anti-HIV efficacy profile of GEN in HIV/HBV coinfected subjects by the proportion of subjects with plasma HIV-1 RNA below 50 copies/mL at Weeks 24 and 48
- To characterize the safety and tolerability profile of GEN in HIV/HBV coinfected subjects at Weeks 24 and 48
- To characterize the biochemical (alanine aminotransferase [ALT] normalization) response at Weeks 24 and 48

- To characterize serological responses (loss of HBV surface antigen [HBsAg] and seroconversion to antibody against HBsAg [anti-HBs], and loss of HBV e-antigen [HBeAg] and seroconversion to antibody against HBeAg [anti-HBe] [for subjects who are HBeAg positive at Day 1]) at Weeks 24 and 48
- To characterize the change in liver fibrosis as assessed by FibroTest® at Weeks 24 and 48

The 24 and 48 Week data were previously presented in the 48 Week Interim Clinical Study Report (CSR). The current CSR provides all data available through the end of the study for all subjects who continued to receive GEN in the Extension Phase (post Week 48 visit).

**Methodology:** This was an open-label, single-arm, multicenter, dual-cohort study to assess the safety, efficacy, and tolerability of GEN in HIV/HBV coinfected subjects through 48 weeks.

Eligible subjects were enrolled into 1 of the following 2 cohorts:

- Cohort 1 (Treatment-naive): HIV/HBV coinfected adults who were HIV and HBV treatment-naive
- Cohort 2 (HIV-suppressed): HIV/HBV coinfected adults who were HIV suppressed (with or without suppression of HBV DNA)

After 48 weeks, all subjects could elect to continue to receive GEN during an Extension Phase and attend visits every 12 weeks until it became commercially available. Subjects who did not want to continue to participate were required to complete a 30-day follow-up visit.

**Number of Subjects (Planned and Analyzed):**
Planned: Up to 125 subjects (up to 50 subjects in Cohort 1 and up to 75 subjects in Cohort 2)
Enrolled: 79 (4 subjects in Cohort 1 and 75 subjects in Cohort 2)
Safety Analysis Set: 77 (3 subjects in Cohort 1 and 74 subjects in Cohort 2)
Full Analysis Set (FAS): 75 (3 subjects in Cohort 1 and 72 subjects in Cohort 2)

**Diagnosis and Main Criteria for Inclusion**: Eligible subjects were HIV and HBV (chronic) coinfected men and nonpregnant and nonlactating women ≥ 18 years of age with a cluster determinant 4 positive (CD4) count > 200 cells/μL, ALT ≤ 10 × upper limit of normal (ULN), total bilirubin ≤ 2.5 mg/dL, international normalized ratio (INR) ≤ 1.5, albumin ≥ 3 g/dL, and Screening creatinine clearance by Cockcroft-Gault of ≥ 50 mL/min, no evidence of cirrhosis or hepatocellular carcinoma, and hepatitis C virus (HCV) and hepatitis D virus (HDV) negative.

Subjects in Cohort 1 were required to have no current or prior anti-HIV treatment, no current or prior anti-HBV treatment, plasma HIV-1 RNA ≥ 500 copies/mL, HIV sensitive to FTC and tenofovir disoproxil fumarate (TDF), and HBV DNA ≥ 3 $\log_{10}$ IU/mL and < 9 $\log_{10}$ IU/mL.

Subjects in Cohort 2 must have received a current antiretroviral (ARV) regimen for at least 4 consecutive months with no current or prior regimen containing 3 active anti-HBV agents, maintained plasma HIV-1 RNA < 50 copies/mL for 6 consecutive months before Screening, and had HBV DNA < 9 $\log_{10}$ IU/mL.

**Duration of Treatment:** 48 weeks of treatment followed by an optional Extension Phase in which all subjects continued to receive GEN until it became commercially available.

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

FDC tablet of GEN (150/150/200/10 mg) administered orally once daily with food.

Lot Numbers: CP1310B1, CP1311B1, CP1313B1, CP1403B1, CP1502B1

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

**Criteria for Evaluation:**

**Efficacy:**

The following endpoints were examined in the final analysis:

- The proportion of subjects with HBsAg loss at postbaseline visits
- The proportion of subjects with HBsAg seroconversion to HBsAb at postbaseline visits
- The proportion of subjects with HBeAg loss at postbaseline visits
- The proportion of subjects with HBeAg seroconversion to anti-HBe at postbaseline visits
- The proportion of subjects with ALT normalization at postbaseline visits
- The change from baseline in CD4 cell count at postbaseline visits
- The change from baseline in CD4% at postbaseline visits
- The proportion of subjects with HIV-1 RNA < 50 copies/mL and HIV-1 RNA < 20 copies/mL at postbaseline visits as defined by Missing = Excluded (M = E) analysis.
- The proportion of subjects with HBV DNA < 29 IU/mL and HBV DNA < 20 IU/mL at postbaseline visits as defined by M = E analysis.

**Pharmacokinetics**:

No pharmacokinetic (PK) analyses were performed for this report.

**Safety:**

Safety assessments for the final analysis included the following: adverse events (AEs), vital signs, electrocardiogram (ECG), weight, concomitant medications, and clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy testing).

Bone safety was assessed with fracture events and the change from baseline at each visit for the following bone biomarkers: serum C-type collagen sequence (CTX), procollagen type 1 N-terminal propeptide (P1NP), and parathyroid hormone (PTH).

Renal safety was assessed with renal events and the change from baseline at each visit for the following renal parameters: serum creatinine, serum cystatin C, estimated glomerular filtration rate using the Cockcroft-Gault equation ($eGFR_{CG}$), eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) serum cystatin C method ($eGFR_{CKD\text{-}EPI\ cystatin\ C)}$, eGFR using the CKD-EPI serum creatinine method ($eGFR_{CKD\text{-}EPI\ creatinine}$), proteinuria, urine retinol binding protein (RBP) to creatinine ratio, urine beta-2-microglobin to creatinine ratio, urine protein to creatinine ratio (UPCR), and urine albumin to creatinine ratio (UACR).

Liver safety was assessed with hepatic events, hepatic flare (ALT flare), and liver enzyme values, alone or in combination, above the ULN.

**Statistical Methods:**

This was a single-arm, 2-cohort study. There were no plans to compare efficacy or safety data between the 2 cohorts.

**Efficacy:**

The FAS was the primary efficacy analysis set and included all subjects who were enrolled into the study, received at least 1 dose of study drug, had at least 1 post-Day 1 plasma HBV DNA or HIV-1 RNA result while on study drug, and had no major protocol violations of eligibility criteria. Descriptive statistics were used to characterize the efficacy profile of each cohort in the study.

The efficacy analyses with respect to the primary efficacy endpoint (at Week 24) and the secondary efficacy endpoints at Week 48 were performed in the Week 24 and Week 48 interim analyses and are not repeated in the final analysis.

Virologic outcome data were summarized using frequency counts and percentages using the M = E approach in which all missing data were excluded in the computation of virologic response.

Serology response and ALT outcomes were summarized based on observed data (M = E). By-visit summaries of the percentage of subjects with ALT within normal range (regardless of baseline ALT) and the percentage of subjects with ALT normalization (who had ALT > ULN at baseline) were provided.

The changes in CD4 cell count and CD4% was based on observed (ie, missing data were excluded), on-treatment data (ie, up to 1 day after the last dose date of study drug).

**Pharmacokinetics:**

No PK analyses were performed for this report.

**Safety:**

The Safety Analysis Set included all enrolled subjects who received at least 1 dose of study drug and was the primary analysis set for all safety analyses. All safety data collected on or after the date of the first dose of study drug up to the last dose date of study drug plus 30 days were summarized by cohort, except for proteinuria by quantitative assessment based on on-treatment data (up to 1 day after the last dose date of study drug).

The safety assessments listed above under Criteria for Evaluation were summarized using descriptive statistics. Categorical data were presented as number and percentage.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. Treatment-emergent AEs were defined as: (1) any AEs with onset date on or after the study drug start date and no later than 30 days after the study drug stop date; or (2) any AEs that resulted in permanent study drug discontinuation. Summaries (number and percentage of subjects) of treatment-emergent AEs (by system organ class [SOC], high-level term, and preferred term [PT]) were provided by cohort.

The subject incidence of fracture events was summarized by cohort based on selected PTs from the Standardized MedDRA Query of Osteoporosis/Osteopenia alone and combined with PTs from the high level group term of Fractures from MedDRA.

Laboratory data were summarized based on values reported in conventional units. For the lipid panel and glucose, only measurements under fasting status were summarized. P-values were obtained from the Wilcoxon Signed-Rank test for subjects in Cohort 2 for the change (or percentage change) from baseline in the following parameters: (1) fasting lipid and glucose data, (2) bone biomarkers.

**SUMMARY OF RESULTS:**

**Subject Disposition and Demographics:**

A total of 79 subjects (75 Cohort 2 subjects, 4 Cohort 1 subjects) were enrolled in the study, and 77 subjects received at least 1 dose of study drug (74 Cohort 2 subjects, 3 Cohort 1 subjects) (Section 15.1, Table 1.1). Forty-six subjects (59.7%) (44 [59.5%] Cohort 2, 2 [66.7%] Cohort 1) received treatment for ≥ 96 Weeks (672 days) (Section 15.1, Table 3.1).

A total of 66 subjects (85.7%) completed 48 weeks of study treatment (64 [86.5%] Cohort 2, 2 [66.7%] Cohort 1). Reasons for discontinuing treatment were as follows: withdrawal of consent (5 subjects [6.5%]), lost to follow-up (3 subjects [3.9%]), AE (1 subject [1.3%]), lack of efficacy (1 subject [1.3%]), or noncompliance (1 subject [1.3%]). Sixty-three subjects (81.8%) went on to receive commercial GEN (61 [82.4%] Cohort 2, 2 [66.7%] Cohort 1 (Section 15.1, Table 1.1).

***Cohort 2: HIV-Suppressed Subjects***

The majority of the 74 subjects were male (91.9%) and < 65 years of age (97.3%; median [range]: 51 years [28 to 67]). The most common races were white (67.6%), black (18.9%), and Asian (9.5%). Most subjects (83.8%) were not Hispanic/Latino. The median (Q1, Q3) baseline BMI was 25.4 (23.1, 28.3) $kg/m^2$ (Section 15.1, Table 2.1.1).

The baseline HIV-1 RNA level was < 50 copies/mL for all except 1 subject (98.6%). The median (Q1, Q3) baseline CD4 count was 611 (440, 783) cells/μL. Most of the subjects (57 subjects [77.0%]) were asymptomatic, 4 subjects (5.4%) were symptomatic, and 13 subjects (17.6%) had acquired immunodeficiency syndrome (AIDS) (Section 15.1, Table 2.2.1.1).

The median (Q1, Q3) baseline $eGFR_{CG}$ was 93.9 (77.1, 115.7) mL/min. Nine subjects (12.2%) had proteinuria (Grade 1 or 2 by dipstick).

Most subjects (86.5%) had a baseline HBV DNA level < 29 IU/mL. The median (Q1, Q3) baseline ALT level was 26 (19, 35) U/L, with levels ≤ 1.0 ULN for most subjects (86.5%). All except 3 subjects were HBsAg positive (71 subjects; 95.9%). One of the 3 subjects was HBsAg positive at screening, negative at baseline, and then positive at the next on-treatment assessment (Week 12) (Appendix 16.2, Listing 4.3). The other 2 subjects were HBsAg negative and had no other evidence of HBV infection; therefore, these 2 subjects were excluded from the FAS (Appendix 16.2, Listing 1.3). Thirty subjects (40.5%) were HBeAg positive. The median (Q1, Q3) baseline FibroTest score was 0.35 (0.21, 0.54) (Section 15.1, Table 2.2.2.1).

The most common ARV regimens at baseline were efavirenz (EFV)/FTC/TDF (16 subjects [21.6%]), raltegravir (RAL)+FTC/TDF (13 subjects [17.6%]), and E/C/F/TDF (Stribild®) (11 subjects [14.9%]). Seventy-one of 74 subjects (95.9%) were receiving ARV regimens with anti-HBV activity due to TDF at baseline; the median (Q1, Q3) duration of TDF use prior to baseline was 4.4 (2.0, 7.4) years (n = 70 evaluable subjects) (Section 15.1, Ad Hoc Table req7557.1). One subject was receiving an ARV regimen that included only lamivudine (3TC) as an anti-HBV agent (lopinavir/ritonavir [RTV] + abacavir/3TC). Two subjects were taking ARV regimens without any anti-HBV agent (ie, did not contain TDF, FTC, or 3TC): 1 subject was receiving RAL+ATV+RTV and another subject was on ATV monotherapy (ATV+RTV) (Section 15.1, Table 2.2.1.1).

***Cohort 1: HIV/HBV Treatment-Naive Subjects***

The 3 subjects were all male and under 50 years of age. Two subjects were PPD and 1 subject was PPD (not Hispanic/Latino) (Section 15.1, Table 2.1.1).

For all 3 subjects, the baseline HIV-1 RNA level was ≥ 2.79 log10 copies/mL, CD4 count was ≥ 299 cells/µL, CD4% was ≥ 18.1%, HBV DNA level was ≥ 7.84 log10 IU/mL, and the baseline ALT level was greater than ULN. All 3 subjects were HBeAg positive. No subjects had a moderate or severe FibroTest category at baseline (Section 15.1, Table 2.2.1.1 and 2.2.2.1).

**Efficacy Results:** The efficacy analyses with respect to the primary efficacy endpoint (at Week 24) and the secondary efficacy endpoints at Week 48 were performed in the Week 24 and Week 48 interim analyses and are not repeated in this final analysis.

***Cohort 2: HIV-Suppressed Subjects***

HIV Efficacy

High rates of virologic suppression (HIV-1 RNA <50 copies/mL) were maintained in the Extension Phase, as assessed using the M = E method. At Week 96, 57 out of 60 subjects (95.0%) had HIV-1 RNA <50 copies/mL (Section 15.1, Table 4.3.2).

The mean (SD) baseline CD4 cell count was 636 (258.6) cells/µL. The mean (SD) change in CD4 cell counts at Weeks 72 (N=63) and 96 (N=58) were 31 (178.4) cells/µL and 23 (205.0) cells/µL, respectively (Section 15.1, Table 4.4.2).

The mean (SD) baseline CD4% was 31.5% (8.79%). The mean (SD) CD4% changes from baseline to Weeks 72 (N=63) and 96 (N=58) were 0.7% (3.80%) and 0.3% (4.60%), (Section 15.1, Table 4.4.3).

HBV Efficacy

High rates of HBV suppression were maintained throughout the Extension Phase. At Week 96, 59 out of 60 subjects (98.3%) had HBV DNA <29 IU/mL (Section 15.1, Table 4.2.4).

During the Extension Phase, of the 70 subjects who were HBsAg positive and anti-HBs negative at baseline, 6 subjects (8.6%) experienced HBsAg loss by Week 72 and 4 of these subjects (5.7%) also achieved seroconversion to anti-HBs. By Week 96, 6 subjects (8.6%) experienced HBsAg loss and 4 of these subjects (5.7%) also achieved seroconversion to anti-HBs (Section 15.1, Table 4.2.5.1).

Of the 30 subjects who were HBeAg positive and anti-HBe negative at baseline, 2 subjects (6.7%) experienced HBeAg loss and 1 of these (3.3%) achieved seroconversion to anti-HBe by Week 72. By Week 96, 2 subjects (6.7%) experienced HBeAg loss and 1 of these (3.3%) achieved seroconversion to anti-HBe (Section 15.1, Table 4.2.5.1).

Ten subjects (13.9%) had ALT values > ULN at baseline; of those subjects, 4 (40.0%) achieved ALT normalization at Week 72 and 5 subjects (50.0%) achieved ALT normalization at Week 96 (Section 15.1, Table 4.2.6.1). Using the M = E approach, 4 of 8 subjects (50.0%) at Week 72 and 5 out of 7 subjects (71.4%) at Week 96 achieved ALT normalization (Section 15.1, Table 4.2.6.3).

***Cohort 1: HIV/HBV Treatment-Naive Subjects***

HIV Efficacy

Only 3 subjects were enrolled in this cohort. Two subjects continued in the Extension Phase from Week 48 to Week 108 and remained virologically suppressed (HIV-1 RNA <50 copies/mL) (Section 15.1, Table 4.3.2).

CD4 cell counts and CD4% increased from baseline during the Extension Phase (Section 15.1, Tables 4.4.2 and Table 4.4.3).

HBV Efficacy

From Week 48 to Week 108, both subjects had HBV DNA < 29 IU/mL (Section 15.1, Table 4.2.4).

No subjects experienced HBsAg loss or seroconversion to anti-HBs at Week 72 or 96. Two subjects experienced HBeAg loss and 1 subject seroconverted to anti-HBe by Week 72 and 96 (Section 15.1, Table 4.2.5.1).

Two out of 3 subjects achieved ALT normalization at Week 48 and this was maintained at Weeks 72 and 96. Data were missing for Week 120 (Section 15.1, Table 4.2.6.1). Using the M = E approach, 2 of 2 subjects (100.0%) at each of Week 72, 96 and 108 achieved ALT normalization (Section 15.1, Table 4.2.6.3).

**Resistance Testing Results:**

A cumulative assessment of all resistance testing for the study is summarized below. Details for resistance testing through Week 48 are provided in a separate Virology Study Report (PC-120-2024).

**HIV Virology Resistance Data**

HIV-1 genotyping of the PR/RT genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for the 3 HIV treatment-naive subjects (Cohort 1) who entered Study GS-US-292-1249. No IN genotyping was conducted at screening in this study. Consistent with enrollment criteria, all enrolled subjects demonstrated full sensitivity to emtricitabine and tenofovir based on the proprietary algorithm from Monogram Biosciences (Appendix16.2, HIV Virology Listing 1). The genotyping results found no NRTI-associated or primary PI-associated resistance mutations in any of the 3 subjects tested. One NNRTI-associated resistance mutation (V106I), which is also a common polymorphism, was observed in 2 of the 3 subjects (PPD and PPD

For this study, no subjects qualified for resistance testing and therefore, no subject was included in the resistance analysis population.

**HBV Virology Resistance Data**

Of the 75 subjects included in the FAS, 10 (13.3%) HBV viremic subjects (HBV DNA ≥ 69 IU/mL) were assessed for preexisting resistance mutations using the INNO-LiPA Multi-DR v2/3 hybridization assay. Of the 10 viremic subjects that qualified for testing, 4 were classified as wild-type (no mutation detected). Five subjects had primary lamivudine resistance (LAM-R) mutations detected. Four of the five subjects with LAM-R were in Cohort 2 (HIV-suppressed), which included treatment experienced subjects. The remaining subject had an rtL180L/M substitution, which by itself does not confer resistance to any known HBV treatment (Appendix 6.2, HBV Virology Listing 1).

Sequence analysis of the pol/RT region was attempted for any subject in Study GS-US-292-1249 who experienced persistent viremia or virologic breakthrough at Week 48 or the end of study, as well as for any subject who discontinued the study at or after Week 24 with HBV DNA ≥ 69 IU/mL. Of the 75 subjects in Study GS-US-292-1249, 2 subjects (2.7%) met one or more of the criteria for sequence analysis, with 1 subject (1.3%) experiencing HBV DNA ≥ 69 IU/mL at Week 48 without virologic breakthrough and 1 subject (1.3%) discontinuing after Week 24 with HBV DNA ≥ 69 IU/mL. The genotypic results showed 1 subject with no change from baseline and one subject with a reversion of a LAM compensatory mutation towards wild-type (Appendix 16.2, HBV Virology Listing 2). Beyond Week 48 no subject qualified for sequence analysis. No subject qualified for phenotypic analysis during the study.

**Pharmacokinetics:** No pharmacokinetic analyses were performed for this report.

**Safety Results:**

***Cohort 2: HIV-Suppressed Subjects***

The median (Q1, Q3) duration of exposure to study drug was 96.0 (94.7, 103.4) weeks. Forty-four subjects (59.5%) received study drug for ≥ 96 weeks (Section 15.1, Table 3.1).

Adverse Events

Sixty-nine subjects (93.2%) had at least 1 treatment-emergent AE. Most subjects had Grade 1 or 2 AEs; 6 subjects (8.1%) had Grade 3 or 4 AEs (Section 15.1, Table 5.1.2 and Table 5.1.4). Twelve subjects (16.2%) had treatment-emergent serious AEs (SAEs) (Section 15.1, Table 5.1.8). None of the SAEs were considered related to study drug. Fourteen subjects (18.9%) had AEs considered related to study drug by the investigator, none of which were Grade 3 or 4 (Section 15.1, Table 5.1.5 and Table 5.1.7). One subject had AEs (Grade 1 weight increased and Grade 2 increased appetite) that led to study drug discontinuation and were considered related to study drug (Section 15.1, Table 5.1.10 and Appendix 16.2, Listing 5.1.6). No subjects died during this study, and no subjects had any Centers for Disease Control Class C AIDS-defining events (Appendix 16.2, Listing 5.1.7 and Listing 5.1.8).

The common AEs (ie, AEs that occurred in ≥ 5% of subjects) were: upper respiratory tract infection (17 subjects [23.0%]), nasopharyngitis (9 subjects [12.2%]), diarrhea (8 subjects [10.8%]), gastroesophageal reflux disease (7 subjects [9.5%]), bronchitis (6 subjects [8.1%]), back pain (6 subjects [8.1%]), sinusitis (5 subjects [6.8%]), allergic rhinitis (5 subjects [6.8%]), pyrexia, chlamydial infection, influenza, gonorrhoea, skin papilloma, benign prostatic hyperplasia), and cough (4 subjects [5.4%] each) (Section 15.1, Table 5.1.2 and 5.1.12). These common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs.

Bone Safety

Three subjects (4.1%) had traumatic fracture events (Section 15.1, Table 5.1.11). One subject had a foot fracture which was nonserious, Grade 1 in severity, and not considered related to study drug. One subject had an upper limb fracture (fractured right elbow) which was nonserious, Grade 2 in severity, and not considered related to study drug. Study drug dosing was not changed, and the AE resolved after approximately 3.2 months. One subject had rib fractures which were serious, Grade 2 in severity, and not considered related to study drug. Study drug dosing was not changed, and the AE resolved after approximately 1.2 months (Appendix 16.2, Listing 5.1.3).

Renal Safety

No subject had an AE of proximal renal tubulopathy or discontinued study drugs due to a renal AE (Section 15.1, Tables 5.1.2 and 5.1.10). Changes from baseline in serum creatinine were minimal throughout the study (Section 15.1, Table 5.7.1). Graded serum creatinine laboratory abnormalities were reported for 8 subjects (10.8%), most of which were Grade 1 (5 subjects [6.8%]) or Grade 2 (2 subjects [2.7%]). One subject had a Grade 3 serum creatinine abnormality at Week 48 (Section 15.1, Table 5.2.1, Appendix 16.2, Listing 5.9.1). Changes from baseline in serum cystatin C or eGFR (by CG or CKD-EPI) were minimal throughout the study (Section 15.1, Tables 5.7.2, 5.7.3, 5.7.4 and 5.7.5).

Median (Q1, Q3) percent changes from baseline in UPCR were as follows: Week 48: −12.8% (−39.2%, 37.4; n = 68); Week 96: −1.1% (−34.1%, 44.0%; n = 59) (Section 15.1, Table 5.8.4). Median (Q1, Q3) percent changes from baseline in UACR were as follows: Week 48: −15.4% (−35.6%, 52.7; n = 68); Week 96: 18.5% (−26.5%, 72.7%; n = 59) (Section 15.1, Table 5.8.5). The urine RBP to creatinine ratio and the urine beta-2-microglobulin to creatinine ratio up to Week 48 are reported in the 48 Week Interim CSR. These parameters were not determined after Week 48.

Hepatic Safety:

No hepatic AEs were reported. The only AE reported in the hepatobiliary disorders SOC was cholelithiasis (Section 15.1, Table 5.1.2). No subject had a confirmed on-treatment ALT flare during the study (Appendix 16.2, Listing 5.10.2). Two subjects (2.7%) had elevated AST or ALT levels > 3 × ULN during this study; 1 subject (1.4%) had AST or ALT levels > 5 × ULN. The liver enzyme abnormalities for this subject were due a nonserious, Grade 1 AE of HCV infection. The HCV infection was not considered related to study drug by the investigator, and was continuing as of the data cutoff date. Neither of these subjects had an elevation in total bilirubin > 1 × ULN (Appendix 16.2, Listings 5.1.1 and 5.10.1). Three subjects (4.1%) had elevations in total bilirubin > 1 × ULN, but ≤ 2 × ULN. No subject had an elevation in ALP > 1.5 × ULN (Section 15.1, Table 5.2.3).

Laboratory Abnormalities:

Most subjects (98.6% [73 subjects]) had at least 1 laboratory abnormality. Most laboratory abnormalities were Grade 1 or 2 in severity. Seventeen subjects (23.0%) and 4 subjects (5.4%) had at least 1 laboratory abnormality with a maximum severity of Grade 3 or 4, respectively (Section 15.1, Table 5.2.1).

There were increases from baseline to Week 96 in total cholesterol, direct low density lipoprotein (LDL) cholesterol, and triglycerides but not in high density lipoprotein (HDL) cholesterol or the total cholesterol to HDL ratio (Section 15.1, Tables 5.5.1 to 5.5.5). In addition, no change from baseline was observed through Week 120 in fasting glucose (Section 15.1, Table 5.5.6). After Week 48, 1 additional subject (1.4%; N = 72) had Grade 3 fasting LDL and 1 additional subject (1.4%; N = 72) had Grade 3 fasting hypercholesterolemia (Section 15.1, Table 5.2.1). None of these abnormalities were reported as AEs.

***Cohort 1: HIV/HBV Treatment-Naive Subjects***

The median (Q1, Q3) duration of exposure to study drug was 107.9 (43.6, 108.7) weeks. Two subjects (66.7%) received study drug for ≥ 96 weeks (Section 15.1, Table 3.1).

Adverse Events

Two of the 3 subjects (66.7%) had at least 1 treatment-emergent AE (Section 15.1, Tables 5.1.1). One subject had a Grade 2 AE and no subjects had a Grade ≥ 3 AE (Section 15.1, Tables 5.1.3 and 5.1.4). None of the AEs was serious, considered related to study drug, or led to study drug discontinuation (Section 15.1, Tables 5.1.8 to 5.1.10). No subjects died during this study, and no subjects had any Centers for Disease Control Class C AIDS-defining events (Appendix 16.2, Listing 5.1.7 and Listing 5.1.8).

Bone Safety:

No subject had a fracture event (Section 15.1, Table 5.1.11). Bone turnover biomarkers (serum CTX and P1NP) up to Week 48 are reported in the 48 Week Interim CSR. Bone turnover biomarkers were not measured after Week48.

Renal Safety:

No subject had an AE in the renal and urinary disorders SOC (Section 15.1, Table 5.1.2).

Hepatic Safety:

No hepatic AEs were reported (Section 15.1, Table 5.1.2). No subject had a confirmed on-treatment ALT flare during the study (Appendix 16.2, Listing 5.10.2).

Laboratory Abnormalities:

No new Grade 3 or 4 laboratory abnormalities were reported after Week 48 (Appendix 16.2, Listing 5.9.2).

**CONCLUSIONS**: Longer term follow-up of subjects through the extension phase confirms the conclusions from the Week 48 analysis and are as follows:

- GEN effectively maintained HIV and HBV virologic suppression for subjects switching from primarily TDF-containing regimens through 96 weeks of treatment.
- The rates of seroconversion to anti-HBs and anti-HBe achieved in treatment-experienced subjects who were HBV antigen positive at baseline were 5.7% and 3.3%, respectively through Week 96.
- ALT normalization in treatment-experienced subjects was achieved in 50.0% of subjects at Week 72 (M = E analysis).

- After 48 weeks of GEN treatment, 2 subjects qualified for HBV sequence analysis, but no mutations associated with resistance to TAF were observed. No subject qualified for HIV or HBV resistance testing in the extension phase of the study. No subjects were found to have emergent resistance to any of the components of GEN.
- GEN was generally well tolerated with no on-study deaths and low incidences of SAEs, discontinuations of study drug due to AEs, and Grade 3 or 4 AEs.
- No subject had an ALT flare, and assessments of other liver-related parameters did not reveal any concerns for increased risk of hepatic clinical outcomes.
- No subjects had an AE of proximal renal tubulopathy or discontinued study drugs due to a renal AE.