FINAL ABBREVIATED CLINICAL STUDY REPORT

Study Title:	A Phase 3b Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of E/C/F/TAF Fixed Dose Combination (FDC) in HIV-1 Infected Subjects on Chronic Hemodialysis
Name of Test Drug:	**Prior to Protocol Amendment 2.1:** Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF [E/C/F/TAF]; Genvoya® [GEN]) **After Protocol Amendment 2.1 (United States [US] Only):** Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/COBI/FTC/TAF [E/C/F/TAF]; Genvoya® [GEN]); Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF [B/F/TAF]; Biktarvy® [BVY])
Dose and Formulation:	**Prior to Protocol Amendment 2.1:** Fixed-dose combination tablet of E/C/F/TAF (150/150/200/10 mg) **After Protocol Amendment 2.1 (US Only):** Fixed-dose combination tablet of E/C/F/TAF (150/150/200/10 mg); fixed-dose combination tablet of B/F/TAF (50/200/25 mg)
Indication:	HIV-1 infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-292-1825
Phase of Development:	Phase 3b
IND No.:	111007
EudraCT No.:	2015-002713-30
ClinicalTrials.gov Identifier:	NCT02600819
Study Start Date:	14 December 2015 (First Subject Screened)
Study End Date:	29 September 2017 (Last Subject Last Observation for the Primary Endpoint) 15 October 2019 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: PPD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	19 February 2020
Previous Report Date:	18 December 2017 (Interim Week 48 Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-292-1825

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

Title of Study: A Phase 3b Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of E/C/F/TAF Fixed Dose Combination (FDC) in HIV-1 Infected Subjects on Chronic Hemodialysis

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled in a total of 26 study sites in 4 countries: 19 in the United States (US), 5 in France, 1 in Austria, and 1 in Germany.

Publications:

Eron JJ Jr, Lelievre JD, Kalayjian R, Slim J, Wurapa AK, Stephens JL, et al. Safety of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-1-infected adults with end-stage renal disease on chronic haemodialysis: an open-label, single-arm, multicentre, phase 3b trial. Lancet HIV 2019;6 (1):e15-e24.

Study Period:

14 December 2015 (First Subject Screened)
29 September 2017 (Last Subject Last Observation for the Primary Endpoint)
15 October 2019 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3b

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) (Genvoya®; GEN) fixed-dose combination (FDC) in HIV-1 infected adults with end-stage renal disease (ESRD) on chronic hemodialysis at Week 48

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of GEN FDC in HIV-1 infected adults with ESRD on chronic hemodialysis at Week 96
- To evaluate the proportion of subjects receiving GEN FDC achieving virologic response (defined as HIV-1 RNA < 50 copies/mL, as defined by the Food and Drug Administration [FDA] snapshot analysis) at Weeks 24, 48, and 96

- To evaluate plasma pharmacokinetics (PK) of EVG, COBI, FTC, TAF, and tenofovir (TFV) in HIV-1 infected patients with ESRD on chronic hemodialysis
- To evaluate the safety and tolerability of bictegravir (BIC, B; previously referred to as GS-9883)/F/TAF (Biktarvy®; BVY) FDC in HIV-1 infected adults with ESRD on chronic hemodialysis in the open-label (OL) extension phase

Results from the primary analysis of the study, performed after all subjects had completed their Week 48 visit or had prematurely discontinued study drug before their Week 48 visit, were described in the Interim Week 48 clinical study report (CSR) (18 December 2017).

This final abbreviated CSR provides efficacy data at and after Week 96 through the end of the study, PK data from the BVY OL extension phase, and a cumulative assessment of the safety data through the end of the study.

Methodology: This was an OL, multicenter, single-group study that assessed the safety, tolerability, PK, and efficacy of GEN dosed once daily in virologically suppressed, HIV-infected adult subjects with ESRD on chronic hemodialysis. All subjects switched from their current antiretroviral (ARV) regimen to GEN on Day 1.

Subjects returned for study visits at Weeks 2, 4, 8, and 12, and then every 12 weeks through Week 96.

After Week 96, as of Protocol Amendment 2.1, subjects in the US continued to take their study drug and may have attended visits every 12 weeks until the End of GEN visit. At Week 96 or the End of GEN visit, subjects in the US discontinued GEN and were given the option to receive BVY in an OL extension phase. Subjects who participated in the BVY OL extension phase returned for study visits at Weeks 4, 12, and every 12 weeks thereafter for at least 48 weeks.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 50 subjects

Analyzed (by analysis set):

- All Enrolled Subjects Analysis Set: 55 subjects
- GEN Safety Analysis Set: 55 subjects
- GEN Full Analysis Set (FAS): 55 subjects
- BVY Enrolled Analysis Set: 10 subjects
- BVY Safety Analysis Set: 10 subjects
- BVY FAS: 10 subjects
- BVY Plasma PK Analysis Set: 10 subjects

Diagnosis and Main Criteria for Inclusion: Eligible subjects were HIV-1 infected adults ≥ 18 years of age with ESRD (estimated glomerular filtration rate calculated using the Cockcroft-Gault equation < 15 mL/min) on chronic hemodialysis for ≥ 6 months prior to screening, HIV-1 RNA < 50 copies/mL on a stable ARV regimen for ≥ 6 consecutive months prior to screening, CD4 cell count ≥ 200 cells/μL, and no documented history of HIV-1 resistance to EVG, FTC, lamivudine (3TC), or TFV.

Duration of Treatment: Subjects were treated with GEN for at least 96 weeks. After at least 96 weeks, subjects who participated in the OL extension phase received BVY for at least 48 weeks.

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

Prior to Protocol Amendment 2.1:

- GEN FDC tablet (E/C/F/TAF 150/150/200/10 mg) administered orally, once daily with food

After Protocol Amendment 2.1 (US Only):

- GEN FDC tablet (E/C/F/TAF 150/150/200/10 mg) administered orally, once daily with food
- BVY FDC tablet (B/F/TAF 50/200/25 mg) administered orally, once daily without regard to food

On the days of hemodialysis, study drug was administered after completion of hemodialysis.

Batch numbers since the Interim Week 48 CSR (18 December 2017):

GEN: CP1605B1

BVY: EN1704B1

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

Criteria for Evaluation:

Efficacy: The protocol-specified efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24, 48, and 96 as determined by the US FDA-defined snapshot algorithm. Results for this endpoint at Weeks 24 and 48 were presented in the Interim Week 48 CSR (18 December 2017).

Efficacy endpoints evaluated for this final analysis were as follows:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 50 copies/mL by visit
- The changes from baseline in CD4 cell count and CD4% by visit

Pharmacokinetics: All plasma PK analyses for the intensive PK substudy were performed as part of the Interim Week 48 CSR (18 December 2017) and were not repeated for this final analysis.

On the days of hemodialysis at Weeks 4, 24, and 48 of the BVY OL extension phase, a sparse timed blood sample was collected from all subjects within 10 minutes prior to hemodialysis initiation. Predose (≤ 30 minutes prior to study drug administration) blood draws for plasma samples were also collected at these visits. Plasma concentrations of BIC were determined.

Safety: The primary endpoint of this study was the incidence of Grade 3 or higher adverse events (AEs) up to Week 48 in subjects who received GEN. The analysis of the primary study endpoint was performed as part of the Interim Week 48 CSR (18 December 2017) and was not repeated for this final analysis. The secondary study endpoint evaluated for this final analysis was the incidence of Grade 3 or higher AEs up to Week 96 in subjects who received GEN.

Baseline and postbaseline safety assessments included monitoring of AEs and concomitant medications, clinical laboratory tests (chemistry, hematology, and pregnancy testing), complete or symptom-directed physical examinations, 12-lead electrocardiograms (ECGs), and vital signs measurements. Body weight was measured and recorded on the visit date.

Other: Medication adherence and healthcare utilization assessments were conducted on Day 1 and at every postbaseline visit through Week 96 of the GEN phase. The Medical Outcome Study 36-Item Short Form Survey (SF-36) and HIV Treatment Satisfaction Questionnaire (HIV-TSQ; comprising status [HIV-TSQs] and change [HIV-TSQc] versions) were administered at specified visits during the GEN phase through Week 96 or the End of GEN visit. The SF-36 and HIV-TSQs questionnaires were also administered at Weeks 4, 24, and 48 of the BVY OL extension phase. All patient-reported outcome assessments were performed at the Early Study Drug Discontinuation visit.

Statistical Methods:

Efficacy: The GEN FAS and BVY FAS, which included all subjects who were enrolled in the study and received at least 1 dose of GEN or BVY, respectively, were the primary analysis sets for efficacy analyses.

The numbers and percentages of subjects with HIV-1 RNA < 50 copies/mL, ≥ 50 copies/mL, or with no virologic data (with reasons) at Week 96 were summarized using the GEN FAS, and the 95% CIs for the percentages of subjects with HIV-1 RNA < 50 copies/mL and ≥ 50 copies/mL were constructed using the Exact method. The same analysis was repeated for the proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm.

The proportion of subjects with HIV-1 RNA < 50 copies/mL was also analyzed using the following 2 methods for imputing missing HIV-1 RNA values: missing = failure (M = F) and missing = excluded (M = E). For the M = F analysis, results were summarized for the GEN FAS. For the M = E analysis, results were summarized for both the GEN FAS and BVY FAS.

Values and changes from baseline in CD4 cell count and changes from baseline in CD4% were summarized at each visit using descriptive statistics (number of subjects, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) based on observed

on-treatment data (ie, up to 1 day after the last dose date of applicable study drug) for the GEN FAS and BVY FAS. In addition, values and changes from baseline in CD4 cell count with missing values imputed using the last observation carried forward method were summarized at each visit.

Pharmacokinetics: Trough concentrations of BIC in plasma were summarized using descriptive statistics (number of subjects, mean, SD, percentage coefficient of variation, median, minimum, maximum, Q1, Q3, and geometric mean) for subjects in the BVY Plasma PK Analysis Set.

Plasma PK sampling details, BIC plasma concentrations, and study drug administration records for plasma PK samples were listed for the BVY OL extension phase.

Safety: The GEN and BVY Safety Analysis Sets, which included all subjects who received at least 1 dose of GEN or BVY, respectively, were the primary analysis sets for the safety analyses.

All safety data collected up to the date of the last dose of study drug plus 30 days were included in the summaries. All safety data were included in data listings. Adverse events were coded using the Medical Dictionary for Regulatory Activities, Version 22.0. Adverse events described in text were treatment emergent unless otherwise specified.

For analysis of the secondary study endpoint, the number and percentage of subjects who had at least 1 Grade 3 or 4 AE up to Week 96 were provided by system organ class and preferred term for the GEN Safety Analysis Set. For subjects who discontinued study drug prior to their Week 96 visit, Grade 3 or 4 AEs up to 30 days after permanent discontinuation of GEN were included.

Laboratory data were summarized using descriptive statistics based on values reported in conventional units. For the lipid panel (ie, total cholesterol, triglycerides, low-density lipoprotein [LDL], high-density lipoprotein [HDL], and total cholesterol to HDL ratio) and glucose, only measurements taken under fasting status were summarized. Sensitivity analyses of fasting lipid tests were also performed using the GEN and BVY Safety Analysis Sets by excluding subjects who took lipid modifying medications.

Other: Results from the HIV-TSQs, HIV-TSQc, and SF-36 questionnaires were summarized for the GEN Safety Analysis Set. Results from the HIV-TSQs and SF-36 questionnaires were also summarized for the BVY Safety Analysis Set. All patient-reported outcome data were listed.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

Of the 75 subjects screened, 55 subjects were enrolled into the study and received at least 1 dose of GEN. Five subjects met all eligibility criteria but were not enrolled; of these 5 subjects, 4 subjects withdrew consent, and 1 subject was outside the visit window for their baseline visit.

Of the 55 subjects treated with study drug, 19 subjects (34.5%) prematurely discontinued GEN, and 16 subjects (29.1%) prematurely discontinued from the study in the GEN phase.

The most common reasons for premature discontinuation of GEN were subject decision (9.1%, 5 subjects), AE (7.3%, 4 subjects), and investigator's discretion (7.3%, 4 subjects). Overall, 36 subjects (65.5%) completed GEN treatment in the GEN phase.

A total of 10 subjects were enrolled into the BVY OL extension phase and received at least 1 dose of BVY. All 10 subjects (100.0%) completed BVY treatment in the BVY OL extension phase.

GEN Phase

The majority of subjects in the GEN Safety Analysis Set were male (76.4%), and the median age was 51 years (range: 23 to 64); the majority of subjects were black (81.8%), and most were not Hispanic or Latino (85.5%). The median (Q1, Q3) value for body mass index (BMI) at baseline was 26.3 (23.5, 30.4) kg/m^2.

This study enrolled a virologically suppressed, HIV-1 infected population; thus, 54 subjects (98.2%) in the GEN Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL. The median (Q1, Q3) baseline CD4 cell count was 515 (387, 672) cells/µL, and 43 subjects (78.2%) had a baseline CD4 cell count ≥ 350 cells/µL. The median (Q1, Q3) baseline CD4% was 30.5% (24.9%, 37.1%). The most common HIV risk factor category was heterosexual sex (60.0%, 33 subjects); 15 subjects (27.3%) reported homosexual sex as an HIV risk factor. The majority of subjects (77.8%) had asymptomatic HIV infection; 10 subjects (18.5%) had been diagnosed with AIDS, and 2 subjects (3.7%) had symptomatic HIV infection. The majority of subjects (78.2%) were hepatitis C virus (HCV) negative.

At baseline, the median (Q1, Q3) duration for which subjects had been treated with hemodialysis was 6 (4, 10) years. A total of 52 subjects (94.5%) in the GEN Safety Analysis Set had a medical history of hypertension, 26 subjects (47.3%) had a medical history of cardiovascular disease, 23 subjects (41.8%) had a medical history of hyperlipidemia, and 15 subjects (27.3%) had a medical history of diabetes. In terms of smoking status, 21 subjects (38.2%) had never smoked, 17 subjects (30.9%) were former smokers, and 17 subjects (30.9%) were current smokers. Prior to switching to GEN, 31 subjects (56.4%) had been receiving an abacavir (ABC)-containing regimen, 16 subjects (29.1%) had been receiving a tenofovir disoproxil fumarate (TDF; Viread®)-containing regimen, and 10 subjects (18.2%) had been receiving an ARV regimen containing neither ABC nor TDF; 36 subjects (65.5%) had been receiving a 3TC-containing regimen, and 4 subjects (7.3%) had been receiving an FTC-containing regimen. Prior to switching to GEN, the majority of subjects (52.7%) had been receiving an ARV regimen containing an integrase strand-transfer inhibitor (INSTI) as a third agent.

BVY OL Extension Phase

The majority of subjects in the BVY Safety Analysis Set were male (80.0%), and median age at baseline of the BVY OL extension phase was 55 years (range: 34 to 63); most subjects were black (90.0%), and most were not Hispanic or Latino (90.0%). The median (Q1, Q3) value for BMI at baseline of the BVY OL extension phase was 26.9 (25.0, 32.2) kg/m^2.

All subjects (100.0%) in the BVY Safety Analysis Set had HIV-1 RNA < 50 copies/mL at baseline of the BVY OL extension phase. The median (Q1, Q3) baseline CD4 cell count was 563 (451, 705) cells/µL, and all 10 subjects (100.0%) had a baseline CD4 cell count

≥ 350 cells/µL. The median (Q1, Q3) baseline CD4% was 32.8% (27.9%, 37.6%). The most common HIV risk factor category was heterosexual sex (60.0%, 6 subjects); 3 subjects (30.0%) reported homosexual sex as an HIV risk factor, 1 subject (10.0%) reported intravenous drug use as an HIV risk factor, and 1 subject (10.0%) had an unknown HIV risk factor. The majority of subjects (80.0%) had asymptomatic HIV infection, and 2 subjects (20.0%) had been diagnosed with AIDS. Among subjects in the BVY Safety Analysis Set, 5 subjects (50.0%) were HCV negative, and 5 subjects (50.0%) were HCV positive.

At the time of study enrollment, the median (Q1, Q3) duration for which subjects had been treated with hemodialysis was 4 (2, 7) years. All 10 subjects (100.0%) in the BVY Safety Analysis Set had a medical history of hypertension, 6 subjects (60.0%) had a medical history of cardiovascular disease, 4 subjects (40.0%) had a medical history of diabetes, and 3 subjects (30.0%) had a medical history of hyperlipidemia. In terms of smoking status, 5 subjects (50.0%) were current smokers, 4 subjects (40.0%) had never smoked, and 1 subject (10.0%) was a former smoker. Prior to switching to GEN, 6 subjects (60.0%) had been receiving an ABC-containing regimen, 3 subjects (30.0%) had been receiving a TDF-containing regimen, and 1 subject (10.0%) had been receiving an ARV regimen containing neither ABC nor TDF; 7 subjects (70.0%) had been receiving a 3TC-containing regimen, and 1 subject (10.0%) had been receiving an FTC-containing regimen. Prior to switching to GEN, the majority of subjects (70.0%) had been receiving an ARV regimen containing an INSTI as a third agent.

Efficacy Results:

GEN Phase

The percentage of subjects in the GEN FAS with HIV-1 RNA < 50 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm was 54.5% (30 of 55 subjects; 95% CI: 40.6% to 68.0%). One subject (1.8%) had HIV-1 RNA ≥ 50 copies/mL at Week 96; this subject discontinued study drug on Day 42 due to lack of efficacy. Retrospective review of historical genotypes for this subject showed preexisting resistance to FTC and EVG.

When assessed using M = F and M = E imputation methods for missing data, the percentage of subjects in the GEN FAS with HIV-1 RNA < 50 copies/mL at Week 96 was 61.8% (34 of 55 subjects; 95% CI: 47.7% to 74.6%) and 100.0% (34 of 34 subjects; 95% CI: 89.7% to 100.0%), respectively. Virologic suppression (HIV-1 RNA < 50 copies/mL) was maintained through the end of the GEN phase.

CD4 cell counts and CD4% remained stable through Week 96. The mean (SD) baseline CD4 cell count and CD4% (GEN FAS; observed data) was 545 (239.2) cells/µL and 31.5% (9.41%), respectively. Mean (SD) changes from baseline in CD4 cell count and CD4% at Week 96 (n = 28) were −35 (218.3) cells/µL and 2.8% (6.37%), respectively. CD4 cell counts and CD4% were maintained through the end of the GEN phase.

BVY OL Extension Phase

When assessed using M = E imputation method for missing data, the percentage of subjects in the BVY FAS with HIV-1 RNA < 50 copies/mL at Week 48 of the BVY OL extension phase was 100.0% (10 of 10 subjects; 95% CI: 69.2% to 100.0%).

CD4 cell counts and CD4% remained stable through Week 48 of the BVY OL extension phase. The mean (SD) baseline CD4 cell count and CD4% (BVY FAS; observed data) was 581 (146.8) cells/µL and 31.9% (7.37%), respectively. Mean (SD) changes from baseline in CD4 cell count and CD4% at Week 48 (n = 9) were −104 (120.8) cells/µL and 1.7% (4.39%), respectively.

Pharmacokinetics Results:

Trough concentrations for BIC (C_{tau}) at Weeks 4, 24, and 48 of the BVY OL extension phase were lower than those observed historically in HIV-1 infected subjects with normal renal function or mild to moderate renal impairment.

Bictegravir C_{tau} remained 4 to 7-fold higher than the $paEC_{95}$ of 162 ng/mL against wild-type HIV-1 virus. Considering sustained virologic suppression was maintained through Week 48 of the BVY OL extension phase, lower BIC C_{tau} is not considered to be clinically relevant.

Safety Results:

Adverse Events

GEN Phase

In relation to the secondary study endpoint, the incidence of Grade 3 or higher AEs up to Week 96, Grade 3 or 4 AEs were reported for 24 of 55 subjects (43.6%) in the GEN Safety Analysis Set.

Overall, 53 subjects (96.4%) had at least 1 AE in the GEN phase, the most common of which were nausea (23.6%, 13 subjects), hyperkalemia (21.8%, 12 subjects), and cough (16.4%, 9 subjects). Most AEs were Grade 1 or 2 in severity; Grade 3 or 4 AEs were reported for 24 subjects (43.6%). Serious adverse events (SAEs) were reported for 36 subjects (65.5%), among which the most common were pneumonia (14.5%, 8 subjects), hyperkalemia (10.9%, 6 subjects), and fluid overload and osteomyelitis (each 7.3%, 4 subjects). Adverse events considered related to study drug were reported for 7 subjects (12.7%), among which only nausea (7.3%, 4 subjects) was reported for > 1 subject; all study drug-related AEs were Grade 1 or 2 in severity. No SAE was considered related to study drug.

Adverse events leading to premature study drug discontinuation were reported for 4 subjects (7.3%) in the GEN phase. One subject had an AE leading to premature study drug discontinuation newly reported for this final analysis; this subject had an ongoing AE of peripheral neuropathy on Day 529 which was considered nonserious and related to study drug. No AE leading to premature study drug discontinuation was reported for > 1 subject.
Three treatment-emergent deaths were reported during the GEN phase; 1 subject died of heart failure and anasarca, 1 subject died of sudden cardiac death, and 1 subject died of cardiac arrest. None of the AEs leading to the deaths were considered related to study drug. No pregnancies were reported during the GEN phase.

Adverse events potentially associated with FTC (ie, among those listed in the FTC prescribing information as having an incidence of ≥ 10%) were reported for 29 subjects (52.7%) in the GEN phase. The most common AEs in this category were nausea (23.6%, 13 subjects), cough (16.4%, 9 subjects), and diarrhea and headache (each 9.1%, 5 subjects). Adverse events in this

category considered related to study drug were reported for 5 subjects (9.1%), while none led to premature discontinuation of study drug.

BVY OL Extension Phase

All 10 subjects (100.0%) in the BVY Safety Analysis Set had at least 1 AE in the BVY OL extension phase. Dyspnea and hypertension were the only AEs reported for > 1 subject in the BVY OL extension phase (each 20.0%, 2 subjects). Most AEs reported were Grade 1 or 2 in severity. One subject (10.0%) had Grade 3 AEs, all of which were assessed as serious and none of which were considered related to BVY. No other subject had a Grade 3 or 4 AE in the BVY OL extension phase. Serious adverse events were reported for 3 subjects (30.0%), and no SAE was reported for > 1 subject. Adverse events considered related to study drug were reported for 1 subject (10.0%; Grade 1 malaise and Grade 2 nausea). No SAE was considered related to study drug. No subject had an AE that led to premature study drug discontinuation, and there were no deaths or pregnancies reported during the BVY OL extension phase.

Adverse events potentially associated with FTC (ie, among those listed in the FTC prescribing information as having an incidence of ≥ 10%) were reported for 4 subjects (40.0%) in the BVY OL extension phase; these comprised cough, headache, insomnia, and nausea (each 10.0%, 1 subject). Nausea was the only AE in this category considered related to study drug, and none of the AEs in this category led to premature discontinuation of study drug.

Cardiovascular and Cerebrovascular Safety

Cardiovascular or cerebrovascular AEs were reported for 1 subject (10.0%) in the BVY Safety Analysis Set. This subject, who had a medical history of ongoing coronary artery disease, had Grade 2 SAEs of angina pectoris and acute myocardial infarction during both the GEN phase and BVY OL extension phase. All of the cardiovascular SAEs were considered not related to study drug and resolved without interruption of study drug.

Hepatic Safety

Hepatic AEs were reported for 1 subject (10.0%) in the BVY Safety Analysis Set. This subject, who had a medical history of cholelithiasis, had Grade 2 and 3 AEs of cholelithiasis during the GEN phase; the Grade 3 cholelithiasis was assessed as serious. Both of the cholelithiasis events were considered not related to study drug and resolved without interruption of study drug.

Laboratory Abnormalities

GEN Phase

There were no clinically relevant changes from baseline in median values for hematology or clinical chemistry parameters through the end of the GEN phase. As is characteristic for patients with ESRD, median values greater than reference values were observed at baseline and postbaseline for amylase, blood urea nitrogen (BUN), parathyroid hormone (PTH), creatinine, and phosphate; otherwise, median values were generally within the relevant reference range.

Most subjects (96.4%, 53 subjects) had at least 1 graded laboratory abnormality in the GEN phase. Grade 1 or 2 laboratory abnormalities were reported for 25 subjects (45.5%), and Grade 3 or 4 laboratory abnormalities were reported for 28 subjects (50.9%).

No subject met Hy's Law criteria in the GEN phase.

BVY OL Extension Phase

There were no clinically relevant changes from baseline of the BVY OL extension phase in median values for hematology or clinical chemistry parameters through the end of the study. As is characteristic for patients with ESRD, median values greater than reference values were observed at baseline and postbaseline of the BVY OL extension phase for amylase, BUN, lipase, PTH, creatinine, and phosphate; otherwise, median values were generally within the relevant reference range.

All subjects (100.0%, 10 subjects) had at least 1 graded laboratory abnormality in the BVY OL extension phase. Grade 1 or 2 laboratory abnormalities were reported for 5 subjects (50.0%), and Grade 3 or 4 laboratory abnormalities were reported for 5 subjects (50.0%).

No subject met Hy's Law criteria in the BVY OL extension phase.

Metabolic Laboratory Parameters

GEN Phase

There were no clinically relevant changes from baseline in median fasting values for total cholesterol, direct LDL, HDL, total cholesterol to HDL ratio, triglycerides, or glucose in serum at Week 96 and through the end of the GEN phase.

BVY OL Extension Phase

There were no clinically relevant changes from baseline in median fasting values for total cholesterol, direct LDL, HDL, total cholesterol to HDL ratio, triglycerides, or glucose in serum at Weeks 24 and 48 of the BVY OL extension phase.

Other Observations Related to Safety

GEN Phase

There were no clinically relevant changes from baseline in median values for vital signs or body weight. Two subjects (1 subject with a normal ECG at baseline and 1 subject with an abnormal [not clinically significant] ECG at baseline) had clinically significant abnormal ECGs at Week 96 of the GEN phase, both of which were reported as nonserious AEs considered not related to study drug. One additional subject, who had an abnormal (not clinically significant) ECG at baseline and a clinically significant prolonged QT at Week 48, had a normal ECG at Week 96.

BVY OL Extension Phase

There were no clinically relevant changes from baseline of the BVY OL extension phase in median values for vital signs or body weight. No subject had a clinically significant abnormal ECG at Week 48 of the BVY OL extension phase.

Other:

GEN Phase

Overall, up to Week 96 of the GEN phase, the majority of subjects underwent hospitalization (74.5%, 41 subjects), but the majority did not have any unplanned visits for a healthcare issue (65.4%, 36 subjects) or unplanned specialty care provider visits (61.8%, 34 subjects).

In terms of treatment satisfaction as measured using the HIV-TSQ, for the HIV-TSQs (maximum possible score of 60), the mean (SD) total treatment satisfaction score at baseline for the GEN phase was 52.9 (7.57) (median [Q1, Q3] was 55.0 [48.0, 60.0]); at Week 96, the mean (SD) total treatment satisfaction score was 57.4 (5.00) (median [Q1, Q3] was 60.0 [57.0, 60.0]). The percentage of subjects who were very satisfied with their current treatment at baseline and at Week 96 was 65.5% (36 of 55 subjects) and 82.4% (28 of 34 subjects), respectively.

For the HIV-TSQc (maximum possible score of 30), the mean (SD) total treatment satisfaction score at Week 96 was 27.4 (4.72) (median [Q1, Q3] was 30.0 [26.0, 30.0]). The percentage of subjects at Week 96 who were much more satisfied with their treatment was 85.7% (30 of 35 subjects). The interpretation of results obtained in the GEN phase after Week 96 was limited since only a few subjects had data for the HIV-TSQs (4 subjects) and HIV-TSQc (1 subject) at Week 120.

Scores for each of the SF-36 subdomains remained consistent through Week 96 of the GEN phase or, in 2 cases (physical functioning and role functioning [physical]), showed an improvement. Median composite physical component and mental component summary scores remained consistent through Week 96 of the GEN phase. The interpretation of results obtained in the GEN phase after Week 96 was limited since only 5 subjects had data at Week 120.

BVY OL Extension Phase

In terms of treatment satisfaction as measured using the HIV-TSQ, for the HIV-TSQs (maximum possible score of 60), the mean (SD) total treatment satisfaction score at baseline for the BVY OL extension phase was 57.5 (2.32) (median [Q1, Q3] was 58.0 [57.0, 59.0]); at Week 48, the mean (SD) total was 57.7 (3.12) (median [Q1, Q3] was 59.0 [58.0, 60.0]).

Scores for the SF-36 subdomains of general health and mental health remained consistent through Week 48 of the BVY OL extension phase. Decreases from baseline at Week 48 of the BVY OL extension phase were observed in the scores for the physical functioning, role functioning (physical), role functioning (emotional), bodily pain, vitality, and social functioning subdomains. Median composite physical component and mental component summary scores remained consistent through Week 48 of the BVY OL extension phase.

CONCLUSIONS:

GEN Phase

Follow-up of subjects beyond Week 48, at and after Week 96 through the end of the study confirms the conclusions from the Week 48 analysis and are as follows:

- Virologic suppression (HIV-1 RNA < 50 copies/mL) was maintained, and CD4 cell counts remained stable in virologically suppressed, HIV-1 infected adult subjects with ESRD on chronic hemodialysis who switched to GEN.
- GEN was generally well tolerated by HIV-1 infected adult subjects with ESRD on chronic hemodialysis. Common AEs were generally consistent with those expected in the study population.

BVY OL Extension Phase

For subjects given the option to receive BVY in an OL extension phase for at least 48 weeks, the conclusions are as follows:

- Virologic suppression (HIV-1 RNA < 50 copies/mL) was maintained, and CD4 cell counts remained stable in virologically suppressed, HIV-1 infected adult subjects with ESRD on chronic hemodialysis who switched to BVY.
- BVY was generally well tolerated by HIV-1 infected adult subjects with ESRD on chronic hemodialysis.
- Lower BIC trough concentrations in HIV-1 infected adult subjects with ESRD were not considered to be clinically relevant.