FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF) or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women
Name of Test Drug:	Bictegravir (previously referred to as GS-9883)/Emtricitabine/ Tenofovir Alafenamide (BVY; Biktarvy® [BVY])
Dose and Formulation:	Fixed-dose combination tablet containing 50 mg bictegravir (BIC, B), 200 mg emtricitabine (FTC, F), and 25 mg tenofovir alafenamide (TAF)
Indication:	HIV-1 infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-380-1961
Phase of Development:	Phase 3
IND No.:	125589
EudraCT No.:	Not Applicable
ClinicalTrials.gov Identifier:	NCT02652624
Study Start Date:	19 February 2016 (First Subject Screened)
Study End Date:	09 October 2017 (Last Subject Last Observation for the Primary Endpoint) 26 November 2018 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Cissy Kityo, MBChB, MSc Affiliation: PPD
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Report Date:	01 April 2019
Previous Report Date(s):	07 February 2018 (Week 48 Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-380-1961
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Randomized, Open Label Study to Evaluate the Safety and Efficacy of Switching to a Fixed Dose Combination (FDC) of GS-9883/Emtricitabine/Tenofovir Alafenamide (GS 9883/F/TAF) from Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF), Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (E/C/F/TDF), or Atazanavir + Ritonavir + Emtricitabine/Tenofovir Disoproxil Fumarate (ATV+RTV+FTC/TDF) in Virologically Suppressed HIV-1 Infected Women

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled and treated at 58 sites in the United States (30, including 1 site in Puerto Rico), the Russian Federation (19), Thailand (6), the Dominican Republic (2), and Uganda (1).

Publications: There were no publications at the time of this clinical study report (CSR).

Study Period:

19 February 2016 (First Subject Screened)
09 October 2017 (Last Subject Last Observation for the Primary Endpoint)
26 November 2018 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To evaluate the efficacy of switching to an FDC of bictegravir (BIC, B; previously referred to as GS-9883)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (B/F/TAF, Biktarvy® [BVY]) versus continuing on a regimen consisting of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF, Genvoya®), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF, Stribild®), or atazanavir (ATV) + ritonavir (RTV) + emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada®) in virologically suppressed HIV-1 infected women as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

The secondary objective of this study was as follows:

- To evaluate the safety and tolerability of the treatment groups through Week 48.
- The primary objective and some secondary and tertiary objectives were addressed in the Week 48 interim clinical study report (CSR) and are not repeated in this report. The current report describes available efficacy and safety data through the end of the study.

Methodology: This is a randomized, open-label, multicenter, active-controlled study to evaluate the safety and efficacy of switching to an FDC of BVY in HIV-1 infected female subjects who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF for ≥ 12 consecutive weeks prior to screening.

All subjects from predefined Gilead Sciences (Gilead) studies who were HIV-1 infected women and who were virologically suppressed may have been eligible to enroll. These studies were: Study GS-US-236-0128 (after completion of the Week 48 open-label extension [OLE] or any post-Week 48 OLE visit), Study GS-US-292-0109 (after completion of the Week 96 visit or any post-Week 96 visits), or Studies GS-US-292-0104 or GS-US-292-0111 (after completion of the Week 144 visit or any post-Week 144 visits).

Subjects who provided written consent and met all eligibility criteria were randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

Treatment Group 1 (BVY): Switched to BVY administered orally once daily without regard to food (n = 235)

Treatment Group 2 (Stay on Baseline Regimen [SBR]): Remained on current antiretroviral (ARV) regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF administered orally once daily with food (n = 237)

Randomization was stratified by the prior treatment regimen group (ie, E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF) at screening.

Subjects were treated for at least 48 weeks. At each subject's Week 48 visit, subjects in countries where BVY was not available were given the option to receive BVY for an additional 48 weeks (with study visits every 12 weeks), or until the product became accessible to subjects through an access program, or until Gilead elected to discontinue the study in that country, whichever occurred first. Subjects who completed the study through the Week 48 visit and did not participate further in the study were required to return to the clinic 30 days after the Week 48 visit for a 30-day follow-up visit.

This report describes the results after all subjects either completed the study or prematurely discontinued the study.

Number of Subjects (Planned and Analyzed):
Planned: approximately 470 subjects (235 subjects in each treatment group)
Analyzed (by analysis set):

	BVY	SBR	Total
All Randomized Analysis Set	235	237	472
Subjects in All BVY Analysis Set	234	228	462

SBR = stay on baseline regimen

Diagnosis and Main Criteria for Inclusion: Eligible subjects were medically stable HIV-1 infected women who met the following criteria: on a stable once-daily ARV regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF with documented HIV-1 RNA < 50 copies/mL for ≥ 12 weeks preceding and at the screening visit; estimated glomerular filtration rate (eGRF) ≥ 50 mL/min using the Cockcroft-Gault method ($eGRF_{CG}$); and no documented or suspected resistance to FTC, tenofovir (TFV), ATV, or elvitegravir (EVG), including but not limited to the reverse transcriptase resistance mutations K65R and M184V/I. Subjects with chronic hepatitis B infection or chronic hepatitis C infection were permitted to enter the study.

Duration of Treatment: At least 48 weeks, up to a maximum of 96 weeks.

Test Product, Dose, Mode of Administration, and Batch No.: BVY (50/200/25 mg) FDC administered orally once daily without regard to food

Batch Numbers: EN1504B1, EN1603B2, EN1604B2, EN1605B2, EN1609B1, EN1610B2

Reference Therapy, Dose, Mode of Administration, and Batch No.: Current ARV drug regimen consisting of E/C/F/TAF, E/C/F/TDF, or ATV+RTV+FTC/TDF administered orally once daily with food.

E/C/F/TAF Batch Numbers: CP1503B1, CP1506B1, CP1603B1, CP1604B1

E/C/F/TDF Batch Numbers: BK1401B1, 005790, VCXP

ATV Batch Numbers: 5A88555A, 5M60157A

RTV Batch Numbers: 1041437, 1065083

FTC/TDF Batch Numbers: 004483

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the modified United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm.

The secondary efficacy endpoints included the following:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the modified US FDA-defined snapshot algorithm
- The change from baseline in CD4 cell count at Week 48

The tertiary efficacy endpoints included:

- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 48 as determined by the modified US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by 2 different missing data imputation methods
- The change from baseline in CD4 percentage (%) at Week 48

Pharmacokinetics: No pharmacokinetic (PK) assessments were performed for this report. Pharmacokinetic analyses were reported in the GS-US-380-1961 Week 48 CSR.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications; clinical laboratory analyses including hematology, chemistry, metabolic parameters, urinalysis, markers of renal function (urine albumin to creatinine ratio [UACR], urine retinol-binding protein [RBP] to creatinine ratio and urine beta-2-microglobulin to creatinine ratio), hepatitis B and C virus (HBV and HCV) monitoring, and pregnancy tests; vital sign measurements; electrocardiograms (ECGs), and complete and symptom-directed physical examinations.

Statistical Methods:

Efficacy: Analyses of the proportions of subjects determined by the modified US FDA-defined Snapshot Algorithm (the primary efficacy endpoint at Week 48 and part of the secondary and tertiary efficacy endpoints) were performed in the Week 48 interim analyses and were not repeated in this final analysis.

For this final analysis, the primary analysis set for all efficacy analyses was the All BVY Analysis Set, which included all subjects who were randomized and received at least 1 dose of BVY during the randomized phase of the study or during the extension phase of the study. The proportion of subjects with HIV-1 RNA < 50 copies/mL was analyzed using the Missing = Excluded (M = E) approach for imputing missing HIV-1 RNA values. All missing data were excluded in the computation of the percentages (ie, missing data points were excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit was the number of subjects in the All BVY Analysis Set with non-missing HIV-1 RNA value at that visit. For M = E analysis, the number and percentage of subjects with HIV-1 RNA in the following categories was summarized: < 50 copies/mL; < 20 copies/mL (< 20 copies/mL not detectable and < 20 copies/mL detectable); 20 to < 50 copies/mL; 50 to < 200 copies/mL; 200 to < 400 copies/mL; 400 to < 1000 copies/mL; ≥ 1000 copies/mL. The 95% confidence interval (CI) of the proportion of subjects with HIV-1 RNA < 50 copies/mL within each subject group was provided using the Clopper-Pearson Exact method.

CD4 cell count and CD4% were summarized using observed, on-treatment data (ie, data collected up to 1 day after the last dose date of BVY) for subjects in the All BVY Analysis Set.

The changes from baseline in CD4 cell count and CD4% at each visit were summarized by treatment group using descriptive statistics based on observed data (ie, missing data points were excluded) using the All BVY Analysis Set. The mean and 95% CI of change from baseline in CD4 cell count over time was plotted using observed data for the All BVY Analysis Set.

Virology analyses in subjects experiencing virologic failure were performed on any subject in the All BVY Analysis Set with a confirmed viral rebound of HIV-1 RNA ≥ 50 copies/mL with confirmatory HIV-1 RNA ≥ 200 copies/mL, or without confirmation if, at the last visit, the subject did not resuppress while on study drug. Resistance analyses consisted of genotypic and phenotypic analyses of the HIV-1 reverse transcriptase, protease, and integrase genes.

Pharmacokinetics: No PK analyses were performed for this report. Pharmacokinetic analyses are reported in the GS-US-380-1961 Week 48 CSR.

Safety: Adverse event and clinical laboratory data were summarized by treatment group using descriptive statistics. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1.

Preferred terms for defining hepatic events (ie, noninfectious and noncongenital hepatobiliary disorders) and cardiovascular or cerebrovascular events were selected from relevant Standardized MedDRA Queries (SMQs). The number and percentage of subjects with hepatic and cardiovascular or cerebrovascular AEs and hepatic and cardiovascular or cerebrovascular serious AEs (SAEs) by preferred term (PT) were summarized by treatment group.

Laboratory data were summarized based on values reported in conventional units. For the lipid panel and glucose, only measurements under fasting status were summarized.

SUMMARY OF RESULTS:

In the following results sections, subjects within the All BVY Analysis Set who were originally randomized to receive BVY are referred to collectively as the BVY group, and subjects who were originally randomized to stay on their baseline regimen and subsequently switched to BVY in the extension phase are collectively referred to as the SBR-BVY group.

Subject Disposition: Of the 470 subjects who were randomized and treated in the randomized phase of the study, 459 subjects entered the extension phase and received BVY treatment. Eight subjects (BVY 3 subjects, SBR 5 subjects) prematurely discontinued study drug in the randomized phase, and 3 subjects in the SBR group remained in the randomized phase after Week 48 due to pregnancy (Table 15.8.1.3).

Overall, 462 subjects (BVY 234 subjects, SBR-BVY 228 subjects) received BVY in either the randomized or extension phase of the study and comprised the All BVY Analysis Set (Table 15.8.1.3 and Figure 15.8.1). Of those subjects in the All BVY Analysis Set, 97.2% (449 of 462 subjects) completed BVY treatment (BVY 97.0%, 227 of 234 subjects; SBR-BVY 97.4%, 222 of 228 subjects). Overall, 13 subjects (2.8%) prematurely discontinued BVY treatment (BVY 7 subjects [3.0%]; SBR-BVY 6 subjects [2.6%]). The reasons for premature discontinuation of BVY treatment were pregnancy (BVY 4 subjects; SBR-BVY 2 subjects), lost to follow-up (2 subjects in each group), adverse event (SBR-BVY 1 subject), protocol violation (BVY 1 subject), and subject decision (SBR-BVY 1 subject).

Subject Demographics and Baseline Disease Characteristics: All 462 subjects in the BVY Analysis Set were female (100.0%). Most subjects were black (37.0%), white (28.1%), or Asian (21.9%), and most were not Hispanic/Latino (84.6%) (Table 15.8.3.1). Overall, median age was 40 years (range: 21 to 64 years). Median (first quartile [Q1], third quartile [Q3]) body mass index (BMI) overall was 25.6 (22.2, 30.5) kg/m^2.

The study enrolled a virologically suppressed, HIV-infected population; therefore, 99.1% of subjects in the All BVY Analysis Set had baseline HIV-1 RNA < 50 copies/mL (Table 15.8.3.2), and 94.4% had baseline HIV-1 RNA < 20 copies/mL (Table 15.9.1). Overall, the median (Q1, Q3) baseline CD4 cell count was 701 (539, 895) cells/μL, with 81.2% of subjects having a baseline CD4 count ≥ 500 cells/μL. The median (Q1, Q3) baseline CD4% was 36.7% (31.3%, 42.7%).

The most common HIV risk factor was heterosexual sex (98.5% of subjects). The majority of subjects (90.3%) had asymptomatic HIV-1 infection; 7.1% had symptomatic HIV-1 infection, and 2.6% were diagnosed with acquired immunodeficiency syndrome (AIDS) (Table 15.8.3.2). The median (Q1, Q3) $eGFR_{CG}$ at baseline was 99.7 (83.4, 117.2) mL/min.

Demographics and baseline disease characteristics were similar between the BVY and SBR-BVY groups within the All BVY Analysis Set.

Efficacy Results:

Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL

Virologic suppression was maintained in those who switched from their baseline regimen to BVY (SBR-BVY) and for those who remained on BVY in the extension phase of the study. The percentages of subjects with HIV-1 RNA < 50 copies/mL after 48 weeks of BVY treatment were high for subjects in the All BVY Analysis Set, both those originally randomized to BVY (99.6%; 95% CI: 97.6% to 100.0%) and those who switched from their baseline regimen to BVY (SBR-BVY) in the extension phase of the study (98.5%; 95% CI: 95.5% to 99.7%) based on the M = E analysis (Table 15.9.1 and Figure 15.9.1). The percentages of subjects with HIV-1 RNA < 20 copies/mL after 48 weeks of BVY treatment also were high in the BVY (92.6%) and SBR-BVY (91.2%) treatment groups, with the larger proportion in both groups having HIV-1 RNA < 20 copies/mL and undetectable by the assay after 48 weeks of treatment (BVY 72.6%; SBR-BVY 68.0%).

After 96 weeks of BVY treatment, 99.5% (207 of 208) of subjects in the BVY group had HIV-1 RNA < 50 copies/mL, and 95.2% (198 subjects) had HIV-1 RNA < 20 copies/mL. Of those subjects with HIV-1 RNA < 20 copies/mL after 96 weeks of treatment, 76.9% (160 subjects) had undetectable HIV-1 RNA and 18.3% had HIV-1 RNA that was detectable by the assay.

Change from Baseline in CD4

The overall mean (standard deviation [SD]) baseline CD4 cell count in the All BVY Analysis Set was 736 (270.8) cells/µL (BVY 712 [268.1] cells/µL; SBR-BVY 761 [271.9] cells/µL) (Table 15.8.3.2).

CD4 cell counts were maintained in those originally randomized to BVY and those who switched from their baseline regimen to BVY in the extension phase of the study (Table 15.9.2 and Figure 15.9.2). Mean (SD) change from baseline in CD4 cell count after 48 weeks of BVY treatment for the BVY group was 31 (159.6) cells/µL (95% CI: 10 to 51 cells/µL) and for the SBR-BVY group was 31 (177.0) cells/µL (95% CI: 5 to 57 cells/µL).

After 96 weeks of BVY treatment, mean (SD) change from baseline in CD4 cell count was 48 (198.3) cells/µL in the BVY group.

The overall mean (SD) baseline CD4% was 37.1% (8.27%) in the All BVY Analysis Set (BVY 36.6% [8.31%]; SBR-BVY 37.7% [8.21%]) (Table 15.8.3.2). Mean (SD) change from baseline in CD4% after 48 weeks of BVY treatment for the BVY group was 0.8% (3.22%) (95% CI: 0.4% to 1.2%) and in the SBR-BVY group was 0.7% (4.08%) (95% CI: 0.1% to 1.3%) (Table 15.9.3).

After 96 weeks of BVY treatment, mean (SD) change from baseline in CD4% was 1.0% (4.52%) (95% CI: 0.3% to 1.6%) in the BVY group.

Virology Resistance Analysis

Of the 462 treated subjects from the All BVY Analysis Set, 4 subjects were included in the resistance analysis population (RAP) through the end of the study (0.9%; 4 of 462 subjects). There was no treatment-emergent drug resistance development (Virology Listings 1-4). Notably, 1 subject developed M184M/I/V on E/C/F/TAF at Week 48 and subsequently achieved HIV-1 RNA < 50 copies/mL after switching to BVY.

Pharmacokinetics: No PK analyses were performed for this report. Pharmacokinetic analyses are reported in the GS-US-380-1961 Week 48 CSR.

Safety Results:

Exposure to BVY

BVY was well tolerated through a median (Q1, Q3) duration of exposure of 76.6 (53.0, 100.0) weeks overall for the All BVY Analysis Set (BVY 100.0 [96.1, 101.9] weeks and SBR-BVY 53.0 [51.8, 54.0] weeks) (Table 15.11.1.1). A total of 13 subjects prematurely discontinued study drug (BVY 7, SBR-BVY 6) (Table 15.8.1.3).

Treatment-Emergent Adverse Events

Overall, 69.7% (322 of 462) of subjects in the All BVY Analysis Set experienced an AE (BVY 76.5%, 179 of 234 subjects; SBR-BVY 62.7%, 143 of 228 subjects) (Table 15.11.2.1.1). The most commonly reported AEs (> 5% overall) among the 462 subjects in the All BVY Analysis Set were as follows: upper respiratory tract infection (9.5%, 44 subjects), nasopharyngitis (8.9%, 41 subjects), headache (7.1%, 33 subjects), urinary tract infection (6.1%, 28 subjects), and vulvovaginal candidiasis (6.1%, 28 subjects) (Table 15.11.2.1.2.2).

The overall incidence and types of common AEs were consistent with those expected in the study population.

The majority of AEs reported were Grade 1 or Grade 2 in severity. Grade 3 or Grade 4 AEs were reported for 6.7% (31 subjects) overall in the All BVY Analysis Set (BVY 7.3%, 17 subjects; SBR-BVY 6.1%, 14 subjects) (Table 15.11.2.2.2.2). No single Grade 3 or 4 AE occurred in > 3 subjects.

Overall, 5.8% (27 of 462) of subjects experienced AEs assessed by the investigator as related to study drug (BVY 9.8%, 23 subjects; SBR-BVY 1.8%, 4 subjects) (Table 15.11.2.3.1.2). Two subjects in the BVY group experienced Grade 3 AEs assessed by the investigator as related to BVY (dyslipidemia [ongoing] and headache [resolved]); no Grade 4 AEs were assessed as related to BVY. No subjects in the SBR-BVY group experienced Grade 3 or 4 AEs assessed as related to BVY (Table 15.11.2.3.3).

One subject (SBR-BVY) experienced 3 Grade 2 study drug-related AEs (elevated liver function tests) that led to premature discontinuation of BVY treatment (Listing 16.2.7.9). Further detail is provided below (Hepatic Safety). A narrative for this subject is provided in Section 15.2.

No treatment-emergent deaths were reported for the All BVY Analysis Set (Table 15.11.2.1.1).

Serious AEs were reported for 5.2% of subjects (24 of 462 subjects) overall in the All BVY Analysis Set (BVY 6.0%, 14 subjects; SBR-BVY 4.4%, 10 subjects) (Table 15.11.4.1.1.2). No SAE was reported for > 1 subject (Table 15.11.4.1.1.1), and no SAEs were considered related to study drug (Table 15.11.4.1.2). Narratives for all subjects who experienced an SAE are provided in Section 15.2.

Pregnancies

There were 19 subjects who became pregnant while on study (Listing 16.2.8.4). Twelve of these subjects (BVY 8; SBR-BVY 4) were taking BVY or had taken BVY at the time pregnancy was confirmed; 6 of the 12 subjects discontinued study drug prematurely due to pregnancy (BVY 4, SBR-BVY 2) (Listing 16.2.5.2).

Of the 12 subjects who were taking BVY or had taken BVY at the time pregnancy was confirmed, 2 of the 12 subjects (both in the BVY group) underwent elective abortion. Healthy live births were reported for 3 of the 12 subjects. One of the 12 subjects gave birth to an infant with patent urachus which required no intervention and was absent on repeat ultrasound. One of the 12 subjects carried twins, 1 of which died in utero and the other was a still-birth; both of these fetal deaths were reported as SAEs and were considered not related to study drug. This subject had a history of previous fetal loss. Outcomes for the remaining 5 of the 12 subjects were unknown.

Hepatic Safety

Seventeen subjects in the All BVY Analysis Set experienced hepatic AEs (BVY 9 subjects, SBR-BVY 8 subjects) (Table 15.11.2.4.2.1), none of which occurred in more than 4 subjects overall. One subject in the SBR-BVY treatment group experienced 3 Grade 2 hepatic AEs that led to premature discontinuation of study drug after approximately 39 weeks of treatment (alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, and gamma-glutamyltransferase [GGT] increased) (Listing 16.2.7.9). All 3 events were considered related to study drug and resolved after treatment with oral ademetionine (Listing 16.2.4.7).

One subject in each treatment group experienced a hepatic SAE (BVY Grade 3 hepatitis, SBR-BVY Grade 2 acute cholecystitis) (Table 15.11.2.4.2.2). The Grade 3 SAE of hepatitis in the subject in the BVY group occurred in the setting of Grade 3 malaria (treated with quinine, paracetamol, and riamet) and required no interruption of BVY. Neither SAE was considered related to study drug, and both events resolved after appropriate treatment (Listing 16.2.7.5).

There were no clinically relevant changes from baseline in median values for alkaline phosphatase (ALP), ALT, AST, or total bilirubin (Tables 15.11.6.2.8 to 15.11.6.2.10 and Table 15.11.6.2.13), and the majority of liver-related graded laboratory abnormalities were Grade 1 or 2 (Table 15.11.6.4.1).

Five subjects (1.1%) overall had Grade 3 or 4 increases in ALT (1 of which was Grade 4), 4 subjects (0.9%) had Grade 3 or 4 increases in AST (1 of which was Grade 4), and 1 subject (0.2%) had a Grade 3 increase in total bilirubin (Tables 15.11.6.4.1 and 15.11.6.4.2). These laboratory abnormalities were reported as AEs for only 1 subject, and those AEs were considered by the investigator to be not related to study drug. Of the subjects with Grade 3 or 4 ALT and/or AST elevations, 1 subject (BVY group) had concurrent Grade 4 ALT and AST elevations that resolved while on study drug (Listings 16.2.8.1.9.2 and 16.2.5.1). Two subjects (1 in each treatment group) had concurrent Grade 3 ALT and AST elevations. These concurrent Grade 3 ALT/AST elevations resolved while on study drug for 1 of the 2 subjects (who was HCV positive) and occurred at the last visit (Week 96) for the other subject (who started tuberculosis treatment and appropriately stopped study drug when starting therapy with rifampin, isoniazid, pyrazinamide, and ethambutol [RIPE]). In addition, 2 subjects (both in the SBR-BVY group and 1 of whom was HCV positive) had concurrent Grade 3 ALT and Grade 2 AST elevations (1 of which resolved and 1 of which remained Grade 2). One subject (BVY group) had concurrent Grade 3 AST and Grade 2 ALT elevations (and was HCV positive) that resolved while on study drug. The 1 subject (SBR-BVY group) with a Grade 3 increase in total bilirubin had no concurrent ALT/AST elevations, and the bilirubin increase remained Grade 1/2.

There were no Grade 3 or 4 increases in ALP. No subject met Hy's Law criteria (Table 15.11.6.5).

Cardiovascular and Cerebrovascular Safety

Two subjects in the All BVY Analysis Set experienced cardiovascular or cerebrovascular events (Table 15.11.2.4.1.2). One subject in the BVY treatment group experienced a Grade 3 AE of angina pectoris (considered to be an SAE) that occurred concurrently with a Grade 3 SAE of hypertensive crisis, both of which were assessed by the investigator as not related to study drug and resolved after appropriate treatment (Listing 16.2.7.4). One subject with traditional cardiac risk factors of smoking and hypertension in the SBR-BVY treatment group experienced Grade 2 AEs of acute myocardial infarction (MI) (considered to be an SAE) and coronary artery disease, neither of which was considered related to study drug. The acute MI resolved after appropriate treatment, and the coronary artery disease remained ongoing.

Renal Safety

No subject in the All BVY Analysis Set had proximal tubulopathy (including Fanconi syndrome), and no subject discontinued BVY due to a renal and urinary disorder or associated investigation AE (Listing 16.2.7.9). There were no renal SAEs reported (Listing 16.2.7.7).

Median (Q1, Q3) change from baseline in serum creatinine after 48 weeks of treatment for the All BVY Analysis Set overall was 0.03 (−0.04, 0.09) mg/dL; for the BVY and SBR-BVY treatment groups individually, median change from baseline was the same (BVY 0.03 [−0.04, 0.08]; SBR-BVY 0.03 [−0.04, 0.10]) (Table 15.11.6.2.21 and Figure 15.11.2.1).

Median (Q1, Q3) change from baseline in $eGFR_{CG}$ after 48 weeks of treatment for the All BVY Analysis Set overall was −1.8 (−10.2, 7.2) mL/min; for the BVY and SBR-BVY treatment groups individually, median change from baseline was similar (BVY −1.4 [−9.6, 7.2]; SBR-BVY −1.8 [−11.4, 7.8]) (Table 15.11.6.2.22 and Figure 15.11.2.2).

For quantitative measures of albuminuria, median (Q1, Q3) percentage change from baseline in UACR after 48 weeks of treatment for the All BVY Analysis Set overall was –4.0% (-34.7%, 41.2%); for the BVY and SBR-BVY treatment groups individually, median change from baseline was similar (BVY −3.6 [−36.2, 34.8]; SBR-BVY −5.3 [−33.1, 46.5]) (Table 15.11.2.4.3.7).

Median (Q1, Q3) percentage change from baseline in urine RBP to creatinine ratio after 48 weeks of treatment for the All BVY Analysis Set overall was −10.6% (−42.3%, 27.7%); for the BVY and SBR-BVY treatment groups individually, median percentage change from baseline was larger in the SBR-BVY treatment group (–16.0 [–44.8, 18.6]) compared with the BVY group (−6.1 [−39.8, 31.1]) after 48 weeks of treatment (Table 15.11.2.4.3.1).

Median (Q1, Q3) percentage change from baseline in beta-2-microglobulin to creatinine ratio for the All BVY Analysis Set overall was −20.6% (−56.8%, 13.4%); for the BVY and SBR-BVY treatment groups individually, median change from baseline was similar (BVY −20.2 [−56.8, 17.3]; SBR-BVY −20.6 [−55.6, 11.7]) (Table 15.11.2.4.3.4).

Results by prior regimen show that the improvements in RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio for the All BVY Analysis Set were primarily experienced by subjects who switched from TDF-containing regimens (Tables 15.11.2.4.3.2 to 15.11.2.4.3.2 and Tables 15.11.2.4.3.5 to 15.11.2.4.3.6). This difference by prior regimen was not observed for UACR (Tables 15.11.2.4.3.8 to 15.11.2.4.3.9).

Psychiatric Safety

Overall, 5 subjects (1.1%) in the ALL BVY Analysis Set (BVY 2 subjects; SBR-BVY 3 subjects) experienced depressive disorders (Table 15.11.2.1.2.1), 4 of whom had pre-existing psychiatric history and depressive disorders. Two subjects (0.4%), one in each treatment group, experienced AEs of suicidal and self-injurious behavior. Both subjects had a pre-existing psychiatric history, and neither event was considered related to study drug or led to discontinuation of study drug (Listings 16.2.4.4 and 16.2.7.1).

Laboratory Evaluations

Overall, 81.8% of subjects (378 of 462 subjects) in the All BVY Analysis Set experienced a Grade 1, 2, 3, or 4 treatment-emergent laboratory abnormality (Table 15.11.6.4.1). Grade 3 or 4 laboratory abnormalities were reported for 22.1% of the All BVY Analysis Set (BVY 27.4%, 64 of 234 subjects; SBR-BVY 16.7%, 38 of 228 subjects) (Table 15.11.6.4.2). The most commonly occurring Grade 3 or 4 laboratory abnormalities were hematuria (10.6%, 49 subjects), increased fasting low density lipoprotein (LDL) (3.7%, 17 subjects), and increased amylase (2.4%, 11 subjects). Only 1 subject had laboratory abnormalities that were reported as drug-related AEs (Grade 2 ALT increased, AST increased, and GGT increased); this subject is described above in the Hepatic Safety section.

There were no clinically relevant changes from baseline for the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and glucose, or total cholesterol to HDL ratio for the All BVY Analysis Set (Tables 15.11.6.3.1 to 15.11.6.3.5).

The majority of lipid parameter abnormalities were Grade 1 or Grade 2. Grade 3 or 4 abnormalities in lipid parameters were infrequent (Table 15.11.6.4.1). Grade 3 elevations in total cholesterol occurred in 3 subjects (0.7%) overall, and Grade 3 elevations in LDL occurred in 17 subjects (3.7%) overall. There were no Grade 4 elevations in lipid parameters.

Vitals Signs, Body Weight, and Electrocardiograms

There were no clinically relevant changes from baseline in vital signs parameters or body weight within either treatment groups or differences between the 2 treatment groups in median values after 48 weeks of treatment (Tables 15.11.7.1.1 to 15.11.7.1.5, Table 15.11.7.2, and Table 15.11.8).

One subject (SBR-BVY group) in the All BVY Analysis Set had atrial fibrillation with normal mean ventricular response at baseline (Day 1) reported as a Grade 2 AE of ECG abnormal that ultimately resolved after approximately 45 weeks and was considered by the investigator to be not related to study drug. The subject's Week 48 ECG was normal. There were no subjects in either treatment group who shifted from a normal baseline ECG to a clinically significant abnormality after 48 weeks of treatment.

CONCLUSIONS:

Results from the extension phase of the study confirm the efficacy and safety of BVY in subjects switching from their baseline regimen to BVY after 48 weeks (SBR-BVY) and in those receiving continuing treatment with BVY beyond 48 weeks (BVY).

- Virologic suppression and CD4 cell counts were maintained in the All BVY Analysis Set.
- BVY was generally safe and well tolerated through the end of the study.
  - No SAE was reported for > 1 subject, and no SAEs were considered related to study drug.
  - There were no cardiovascular or cerebrovascular AEs that were assessed as related to study drug or led to premature discontinuation of study drug.
  - One subject in the BVY group experienced 3 AEs of elevated ALT, AST, and GGT that were assessed as related to study drug and led to premature discontinuation of study drug. All 3 events resolved. No subject met Hy's Law criteria. No other subjects discontinued study drug prematurely due to an AE.
  - No subject had proximal tubulopathy (including Fanconi syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE. There were no renal SAEs reported.
- No subject in the All BVY Analysis Set developed treatment-emergent drug resistance.