FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed
Name of Test Drug:	Bictegravir (previously referred to as GS-9883)/Emtricitabine/ Tenofovir Alafenamide (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:	Human immunodeficiency virus type 1 (HIV-1) infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-380-1844
Phase of Development:	Phase 3
IND No.:	125589
EudraCT No.:	2015-004025-14
ClinicalTrials.gov Identifier:	NCT02603120
Study Start Date:	11 November 2015 (First Subject Screened)
Study End Date:	09 May 2017 (Last Subject Last Observation for the Primary Endpoint) 23 October 2019 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Peter J Ruane, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Hal Martin, MD, MPH Telephone: PPD Fax: PPD
Report Date:	13 August 2020
Previous Report Date:	23 May 2017 (Week 48 Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-380-1844
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed

Investigators: This was a multicenter study.

Study Centers: Subjects were enrolled and treated at a total of 96 study centers: 3 in Australia, 1 in Belgium, 5 in Canada, 4 in France, 8 in Germany, 1 in Italy, 7 in Spain, 3 in the United Kingdom (UK), and 64 in the United States (US; including Puerto Rico).

Publications:

Andreatta K, Willkom M, Martin R, Chang S, Wei L, Liu H, et al. Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide Maintained HIV-1 RNA Suppression in Participants with Archived Antiretroviral Resistance Including M184V/I. J Antimicrob Chemother 2019.

Molina JM, Ward D, Brar I, Mills A, Stellbrink HJ, Lopez-Cortes L, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. The Lancet HIV 2018a.

Study Period:

11 November 2015 (First Subject Screened)
09 May 2017 (Last Subject Last Observation for the Primary Endpoint)
23 October 2019 (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 from a regimen of dolutegravir (DTG) and abacavir/lamivudine (ABC/3TC) or an FDC of ABC/DTG/3TC 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 DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of the 2 treatment groups through Week 48
- To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48

This report describes the analysis of both the randomized phase and All BVY analysis of the study. For the randomized phase, data for all randomized and treated subjects who had completed their End of Blinded Treatment Visit, or had prematurely discontinued study drug before their End of Blinded Treatment Visit are presented. For the All BVY analysis, data for subjects who were randomized into the randomized phase of the study and received at least 1 dose of BVY in the randomized phase or open-label (OL) extension phase are presented.

Methodology: This was a randomized, double-blind, multicenter, active-control study to evaluate the efficacy, safety, and tolerability of switching to BVY versus continuing DTG and ABC/3TC as the ABC/DTG/3TC FDC in virologically suppressed HIV-1 infected adult subjects who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 consecutive months prior to screening.

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 (50/200/25 mg) FDC tablet + placebo-to-match ABC/DTG/3TC administered orally, once daily, without regard to food (n = 260)
- **Treatment Group 2:** ABC/DTG/3TC (600/50/300 mg) FDC tablet + placebo-to-match BVY administered orally, once daily, without regard to food (n = 260)

Subjects were treated for at least 48 weeks during the blinded treatment phase. After Week 48, all subjects continued to take their blinded study drugs and attended visits every 12 weeks until the End of Blinded Treatment Visit. Once the last subject completed the Week 48 visit and Gilead Sciences (Gilead) completed the Week 48 analyses, all subjects returned to the clinic (preferably within 30 days) for an End of Blinded Treatment Visit. At the End of Blinded Treatment Visit, if safety and efficacy of BVY were demonstrated following review of unblinded data, subjects in a country where BVY was not available were given the option to receive BVY in an OL extension phase for up to 144 weeks, or until the product became accessible to subjects through an access program, or until Gilead elected to discontinue the study in that country.

All subjects who participated in the OL extension phase, without regard to their blinded treatment regimen, returned for study visits at Week 12 OL and every 12 weeks thereafter for up to 144 weeks or until the product became available to subjects. Subjects who completed the study through the End of Blinded Treatment Visit and did not continue on the OL BVY FDC extension phase, were required to return to the clinic 30 days after the End of Blinded Treatment visit for a 30-Day Follow-Up Visit.

Number of Subjects (Planned and Analyzed):
Planned: 520 subjects (260 subjects in each treatment group)
Analyzed (by analysis set):

	BVY	ABC/DTG/3TC	Total
All Randomized Analysis Set	284	283	567
Subjects in Safety Analysis Set	282 (99.3%)	281 (99.3%)	563 (99.3%)
Subjects in Full Analysis Set	282 (99.3%)	281 (99.3%)	563 (99.3%)
Subjects in Hip DXA Analysis Set	256 (90.1%)	265 (93.6%)	521 (91.9%)
Subjects in Spine DXA Analysis Set	256 (90.1%)	262 (92.6%)	518 (91.4%)
Subjects in the All BVY Analysis Set	282 (99.3%)	265 (93.6%)	547 (96.5%)

3TC = lamivudine; ABC = abacavir; BVY = Biktarvy; DTG = dolutegravir; DXA = dual energy x-ray absorptiometry
The denominator for percentages is the number of subjects in the Randomized Analysis Set.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were HIV-1 infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of DTG + ABC/3TC or ABC/DTG/3TC FDC for ≥ 3 consecutive months prior to screening, with no documented resistance to any of the study agents at any time in the past; an estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula ($eGFR_{CG}$); and the absence of chronic hepatitis B virus (HBV) infection.

Duration of Treatment: 48 weeks of randomized, double-blind treatment, followed by an optional OL extension in which all subjects received BVY for up to 144 weeks.

Test Product, Dose, Mode of Administration, and Batch No.: BVY (50/200/25 mg) FDC tablet, plus placebo-to-match ABC/DTG/3TC administered orally, once daily without regard to food.

Batch Numbers:

BVY: EN1503B2, EN1504B1, EN1601B2, EN1602B2, EN1604B2, EN1605B2, EN1608B1, EN1610B2, EN1613B2, and EN1704B1

Placebo-to-match ABC/DTG/3TC: EJ1502B1, EJ1501B1R, EJ1601B1, and EJ1602B1

Reference Therapy, Dose, Mode of Administration, and Batch No.: ABC/DTG/3TC (600/50/300 mg) FDC tablet, plus placebo-to-match BVY administered orally, once daily without regard to food.

Batch Numbers:

ABC/DTG/3TC: EJ1505B1, EJ1508B1, EJ1509B1, EJ1512B1, EJ1514B1, EJ1515B1, EJ1516B1, EJ1519B1, EJ1518B1, EJ1521B1, EJ1517B1, 5ZP2099, 6ZP5798, 6ZP7794, and 7ZP0635

Placebo-to-match BVY: EN1502B1, EN1607B1, and EN1607B2

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 United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm. Other efficacy endpoints evaluated for the Week 48 analysis included the proportions of subjects with HIV-1 RNA < 50 copies/mL and < 20 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm and change from baseline in CD4 cell count at Week 48. These results are presented in the Study GS-US-380-1844 Interim Week 48 clinical study report (CSR).

Efficacy endpoints included in this final analysis are the proportion of subjects with HIV-1 RNA < 50 copies/mL by missing = excluded (M = E) approach, change from baseline in CD4 cell count and CD4%.

Pharmacokinetics: No pharmacokinetic (PK) assessments were performed for this report. The PK analyses are presented in the Study GS-US-380-1844 Interim Week 48 CSR.

Safety: Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses including chemistry, hematology, urinalysis, pregnancy testing, and 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), BMD using dual energy x-ray absorptiometry (DXA) scans, vital signs measurements, electrocardiograms (ECGs), and complete and symptom directed physical examinations.

Other: Other assessments included evaluations of markers of inflammation and immune activation and markers of platelet function, optional genomic testing, and patient reported outcomes (Short Form 36 health survey; HIV Symptoms Distress Module; Work Productivity and Activity Impairment Questionnaire; and Pittsburgh Sleep Quality Index questionnaire).

Statistical Methods:

Efficacy: For this final analysis, the primary analysis set was All BVY Analysis Set, which included all subjects who were randomized into the randomized phase of the study and received at least 1 dose of BVY in the randomized phase or at least 1 dose of BVY in the OL extension phase. The efficacy analyses also used the Full Analysis Set (FAS), which included all subjects who (1) were randomized into the study and (2) received at least 1 dose of study drug.

For M = E analysis, the number and percentage of subjects with HIV-1 RNA in the following categories were 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; and ≥ 1000 copies/mL. For the randomized phase analysis only, p-values and the differences in proportion of subjects with HIV-1 RNA < 50 copies/mL and its 95% CI between treatment groups were calculated based on an unconditional exact method using 2 inverted 1-sided tests. For both the randomized phase and all BVY analyses, the 95% CI for the proportion of subjects with HIV-1 RNA < 50 copies/mL for a treatment group was constructed using the Clopper-Pearson exact method.

The changes from baseline in CD4+ cell count at each visit including visit past Week 48 were summarized by treatment group using descriptive statistics. For the randomized phase analysis, the differences in changes from baseline in CD4+ cell count between the 2 treatment groups and the associated 95% CI were constructed using analysis of variance (ANOVA) models, including treatment group as a fixed effect. No statistical comparisons were made for the all BVY analysis.

A similar analysis was conducted for CD4% using the FAS for the randomized phase analysis and the All BVY Analysis Set for the all BVY analysis.

Virology Resistance: Resistance testing was performed for any subject who received at least 1 dose of study drug, maintained their study drug regimen (or within 72 hours after interruption or discontinuation of study drug), and met 1 of the following virologic failure criteria:

- Virologic rebound: At any visit, a rebound in HIV-1 RNA ≥ 50 copies/mL, which was subsequently confirmed and ≥ 200 copies/mL at the following scheduled or unscheduled visit
- Viremic at final timepoints: Any subject with HIV-1 RNA ≥ 200 copies/mL at Week 48 (primary efficacy endpoint) or study discontinuation who did not meet any of the criteria above was also tested for resistance

HIV-1 proviral reverse transcriptase (RT)/ protease (PR)/ integrase (IN) DNA genotype testing was performed retrospectively from baseline samples. If available, historical PR/RT and/or IN genotypes were also used to evaluate the presence of preexisting substitutions. Historical and retrospective baseline archive PR, RT, and IN sequences were analyzed for the presence of previously identified resistance-associated substitutions to antiretroviral agents.

Pharmacokinetics: No PK assessments were performed for this report. The PK analyses are presented in the Study GS-US-380-1844 Interim Week 48 CSR.

Safety: Safety data were summarized by treatment group using descriptive statistics for the subjects in the Safety Analysis Set for the randomized phase analysis, and the subjects in the All BVY Analysis Set for the all BVY analysis, unless otherwise specified. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1. Adverse

event data were summarized for the All BVY Analysis Set only, except that the summaries for treatment-emergent AEs by system organ class, high level term, and preferred term were also provided for subjects in the Safety Analysis Set. Selected safety endpoints were also analyzed for subjects with HIV/HBV coinfection at baseline, emergent HIV/HBV coinfection while on study drug, subjects with HIV/hepatitis C virus (HCV) coinfection at baseline, and subjects with emergent HIV/HCV coinfection while on study drug.

Preferred terms for defining hepatic events (ie, noninfectious and noncongenital hepatobiliary disorders) and cardiovascular or cerebrovascular events were selected from relevant Standardized MedDRA Query. The number and percentage of subjects with treatment-emergent hepatic and cardiovascular or cerebrovascular AEs and hepatic and cardiovascular or cerebrovascular serious adverse events (SAEs) by PT was summarized for the All BVY Analysis Set.

The percentage change from baseline in hip BMD and spine BMD was summarized by treatment group and visit using descriptive statistics for subjects in the Hip and Spine DXA Analysis Sets, respectively, and compared between the 2 treatment groups at each visit using an ANOVA model, including treatment as a fixed effect.

Laboratory data were summarized based on values reported in conventional units. Summaries of laboratory data were provided for the All BVY Analysis Set only, except that the summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities were provided for subjects in the Safety Analysis Set and All BVY Analysis Set, respectively. For the lipid panel and glucose, only measurements under fasting status were summarized. Descriptive statistics were provided for the following parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, fasting glucose, lipid panel, serum creatinine, $eGFR_{CG}$, urine creatinine, urine RBP to creatinine ratio, beta-2-microglobulin to creatinine ratio, and UACR.

Other: No analyses of optional genomic testing have been conducted or are currently planned at the time of this report. Statistical methods for other assessments including evaluations of markers of inflammation and immune activation and markers of platelet function, and results for patient-reported outcomes assessments may be presented in subsequent analyses.

SUMMARY OF RESULTS:

Subject Disposition and Demographics

Randomized Phase

Of the 646 subjects screened, 567 were randomized to study drugs, as reported in the GS-US-380-1844 Week 48 Interim CSR. Four subjects randomized to study drugs (BVY 2 subjects; ABC/DTG/3TC 2 subjects) did not receive any dose of study drug due to withdrawn consent or protocol violation (Table 15.8.1.2).

Of the 563 subjects who were randomized and treated (BVY 282 subjects; ABC/DTG/3TC 281 subjects), 93.4% of subjects (526 subjects; BVY: 260 subjects, 92.2%; ABC/DTG/3TC: 266 subjects, 94.7%) completed study drugs in the randomized phase, and 6.6% of subjects (37 subjects) prematurely discontinued study drugs (BVY: 22 subjects, 7.8%; ABC/DTG/3TC: 15 subjects, 5.3%). The most common reasons for discontinuation of study

drugs were subject decision (15 subjects; BVY: 6 subjects, 2.1%; ABC/DTG/3TC: 9 subjects, 3.2%), AE (9 subjects; BVY: 6 subjects, 2.1%; ABC/DTG/3TC: 3 subjects, 1.1%), and lost to follow-up (6 subjects; BVY: 4 subjects, 1.4%; ABC/DTG/3TC: 2 subjects, 0.7%) (Table 15.8.1.2).

Demographic and baseline characteristics were similar between the 2 treatment groups. Most subjects were male (88.6%) and not Hispanic/Latino (82.5%). Most subjects were either white (72.9%) or black (21.6%). Median age was 46 years (range: 20 to 71 years). Median (first quartile [Q1], third quartile [Q3]) body mass index (BMI) was 26.1 (23.7, 29.3) kg/m^2 (Table 15.8.3.1.1). Baseline disease characteristics were similar between the 2 treatment groups, except baseline CD4 cell count. The study enrolled a virologically suppressed, HIV-infected population; therefore, 97.7% of subjects in the Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL (BVY: 278 subjects, 98.6%; ABC/DTG/3TC: 272 subjects, 96.8%), and 93.1% had baseline HIV-1 RNA < 20 copies/mL (BVY: 265 subjects, 94.0%; ABC/DTG/3TC: 259 subjects, 92.2%) (Table 15.8.3.2.1 and Table 15.9.2.3.1). Overall, the median (Q1, Q3) baseline CD4 cell count was 695 (510, 910) cells/µL (BVY 732 cells/µL; ABC/DTG/3TC 661 cells/µL, p = 0.011), with approximately three-quarters (76.7%) of subjects having a baseline CD4 count ≥ 500 cells/µL. The median (Q1, Q3) baseline CD4% was 35.7% (28.0%, 41.4%) (Table 15.8.3.2.1).

The most common HIV risk factor was homosexual sex (74.8% of subjects); 21.8% of subjects reported heterosexual sex as an HIV risk factor. The majority of subjects (86.7%) had an asymptomatic HIV-1 infection; 3.2% had a symptomatic HIV-1 infection, and 10.1% were diagnosed with AIDS. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 100.7 (84.6, 120.1) mL/min (Table 15.8.3.2.1).

Subjects in the All BVY Analysis Set

Overall, 547 subjects received at least 1 dose of BVY during either the randomized phase or the OL extension phase and were included in the All BVY Analysis Set (BVY: 282 subjects, 99.3%; ABC/DTG/3TC to BVY: 265 subjects, 93.6%) (Table 15.8.5). Of the 524 subjects treated in the OL extension phase, 97.1% of subjects (509 subjects) completed study drug in the OL extension phase, and 2.9% (15 subjects) prematurely discontinued study drug. The most common reasons for discontinuation of study drug in the OL extension phase were lost to follow-up (5 subjects, 1.0%), subject decision (4 subjects, 0.8%), and investigator's discretion (3 subjects, 0.6%) (Table 15.8.1.2).

For subjects in the All BVY Analysis Set, most subjects were male (89.2%) and not Hispanic/Latino (82.4%). Most subjects were either white (73.0%) or black (21.3%). Median age was 47 years (range: 21 to 71 years) (Table 15.8.3.1.2). Median (Q1, Q3) BMI was 26.1 (23.7, 29.3) kg/m^2. Baseline disease characteristics were generally similar between those subjects who remained on BVY and for those subjects who switched from ABC/DTG/3TC to BVY in the OL extension phase. Overall, 98.9% of subjects in the All BVY Analysis Set had baseline HIV-1 RNA < 50 copies/mL, and 93.1% had baseline HIV-1 RNA < 20 copies/mL (Table 15.8.3.2.2 and Table 15.9.2.3.2). The median (Q1, Q3) baseline CD4 cell count was 709 (536, 905) cells/µL, with approximately three-quarters (79.5%) of subjects having a baseline CD4 count ≥ 500 cells/µL. The median (Q1, Q3) baseline CD4% was 35.5% (28.6%, 41.4%) (Table 15.9.2.5.2).

The most common HIV risk factor was homosexual sex (75.5% of subjects); 21.0% of subjects reported heterosexual sex as an HIV risk factor. The majority of subjects (86.7%) had an asymptomatic HIV-1 infection; 3.3% had a symptomatic HIV-1 infection, and 10.1% were diagnosed with AIDS. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 97.8 (82.6, 117.6) mL/min (Table 15.8.3.2.2).

Efficacy Results:

Randomized Phase

Results from the primary efficacy analysis of Study GS-US-380-1844 demonstrated that switching to BVY was noninferior to maintaining treatment with ABC/DTG/3TC, when administered for 48 weeks to HIV-infected subjects, as assessed using the US FDA-defined snapshot algorithm with HIV-1 RNA ≥ 50 copies/mL. These results are presented in the Study GS-US-380-1844 Interim Week 48 CSR.

The median (Q1, Q3) duration of exposure to study drugs was 61.1 (58.9, 70.0) weeks for the BVY group and 62.9 (59.0, 70.0) weeks for the ABC/DTG/3TC group (Table 15.11.1.1.1). Therefore, Week 60 was selected as the time point to evaluate efficacy beyond Week 48 in the randomized phase for all treatment groups.

Overall, the percentage of subjects with HIV-1 RNA < 50 copies/mL continued to be maintained in both treatment groups through the randomized phase, as assessed using M = E analysis for the subjects in the FAS. The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 60 were as follows: BVY 98.9% (262 of 265 subjects);
ABC/DTG/3TC 99.2% (263 of 265 subjects); 95% CI: −2.7% to 1.7% (Tables 15.9.2.3.1).

CD4 cell counts and CD4% continued to be maintained in both treatment groups. The mean (SD) changes from baseline to Week 60 in CD4 cell counts were as follows: BVY 8 (177.8) cells/μL; ABC/DTG/3TC 28 (186.2) cells/μL; difference in least-squares mean (LSM): −20 cells/μL, 95% CI: −51 to 11 cells/μL (Table 15.9.2.4.1.1). The mean (SD) changes from baseline to Week 60 in CD4% were as follows: BVY, 0.9% (3.78%) and ABC/DTG/3TC −0.1% (4.09%) (difference in LSM: 1.0%, 95% CI: 0.3% to 1.7%; p = 0.004) (Table 15.9.2.5.1).

Subjects in the All BVY Analysis Set

Median (Q1, Q3) duration of exposure to study drugs was 118.5 [107.7, 127.9] weeks for the BVY group, 49.6 [47.4, 60.1] weeks for the ABC/DTG/3TC to BVY group, and 96.0 (48.7, 119.0) weeks for the All BVY group (Table 15.11.1.1.2). Therefore, Weeks 120 (BVY group), 48 (ABC/DTG/3TC to BVY group), and 96 (All BVY group) were selected as the time points to evaluate efficacy for the OL extension phase.

Overall, the percentage of subjects with HIV-1 RNA < 50 copies/mL (as assessed using M = E analysis) continued to be maintained in subjects who remained on BVY and those who switched from ABC/DTG/3TC to BVY during the OL extension phase. The percentages of subjects with HIV-1 RNA < 50 copies/mL (M = E method) at selected time points were as follows: BVY 99.5% (191 of 192 subjects) at Week 120, ABC/DTG/3TC to BVY 99.1% (216 of 218 subjects) at Week 48, and All BVY 100.0% (283 of 283) subjects at Week 96. At Week 144, all 49 subjects who remained in the study (all in the BVY group) had HIV-1 RNA < 50 copies/mL (Table 15.9.2.3.2).

CD4 cell counts and CD4% continued to be maintained in those subjects who remained on BVY and those who switched from ABC/DTG/3TC to BVY during the OL extension phase. The mean (SD) baseline CD4 cell counts were as follows: BVY 752 [302.2] cells/μL, ABC/DTG/3TC to BVY 719 [298.2] cells/μL, and All BVY 736 (300.5) cells/μL. The mean (SD) changes from baseline in CD4 cell counts at selected time points were as follows: BVY 21 (191.8) cells/μL at Week 120; ABC/DTG/3TC to BVY −26 (152.4) cells/μL at Week 48; All BVY 7 (200) cells/μL at Week 96 (Table 15.9.2.4.1.2 and Figure 15.9.2.2.2). The mean (SD) changes from baseline in CD4% at selected time points were as follows: BVY 1.2% (4.35%) at Week 120, ABC/DTG/3TC to BVY 1.2% (3.55%) at Week 48, and All BVY 0.9% (4.22%) at Week 96. At Week 144, the changes from baseline in CD4 cell count and CD4% in the 49 subjects who remained in the study (all in the BVY group) were as follows: CD4 cell count, −3 (209.4) cells/μL; CD4%, 2.2% [4.56%]) (Tables 15.9.2.4.1.2 and 15.9.2.5.2).

Virologic resistance

Pretreatment PR/RT genotypes, derived from cumulative historical genotypes and/or proviral DNA genotyping of baseline samples, were available for 528 of the 563 randomized and treated subjects (93.8%). Exclusion mutations M184V/I and K65R were detected at baseline by retrospective proviral DNA genotyping in 17 (3.2%) and 3 (0.6%) of 528 subjects with pretreatment data, respectively, including 1 subject (0.2%) who had both M184V and K65R substitutions. One or more pre-existing thymidine analog mutations (TAMs) were detected in 36 of 528 subjects with data (6.8%). Pretreatment IN genotypes were available for 503 of 563 subjects (89.3%). Preexisting primary integrase strand-transfer inhibitor (INSTI) resistance substitutions were detected in 17 of 503 subjects with data (3.4%): T97A was detected in 12 subjects (2.4%) and T66I, Y143H, Q148H, N155H, and R263K were detected in 1 subject each (0.2%).

In the All BVY group, 545 of 547 subjects (99.6%) had ≥ 1 on-treatment HIV-1 RNA measurement and 522 of 545 subjects (95.8%) had pretreatment PR/RT genotypic data. Through the end of the study, all subjects with preexisting M184V/I (17 of 17 subjects, 100%) and K65R (3 of 3 subjects, 100%) and 35 of 36 subjects (97.2%) with ≥ 1 preexisting TAM had HIV-1 RNA < 50 copies/mL at their last study visit. Pretreatment IN genotypic data were available for 502 of 545 subjects (92.1%), and all subjects with pre-existing INSTI resistance substitutions who were treated with BVY had HIV-1 RNA < 50 copies/mL at their last study visit (16 of 16 subjects, 100%).

The Resistance Analysis Population (RAP) through Week 48 is presented in the Study GS-US-380-1844 Week 48 virology safety report (PC-380-2004). Following the Week 48 analysis, 2 subjects met the criteria for resistance testing, 1 in the BVY group and the other in the ABC/DTG/3TC group, and neither had treatment-emergent resistance. Of the 547 subjects in the All BVY group, 4 subjects (0.7%) were included in the RAP through the end of the study. No treatment-emergent resistance to BVY was detected throughout the randomized or OL extension phases of the study.

Pharmacokinetics Results: No PK assessments were performed for this final report. Pharmacokinetic results are presented in the Study GS-US-380-1844 Interim Week 48 CSR.

Safety Results:

Randomized Phase

Biktarvy and ABC/DTG/3TC were generally well tolerated in subjects throughout the randomized phase of the study. The median (Q1, Q3) duration of exposure to study drugs was 61.1 (58.9, 70.0) weeks for the BVY group and 62.9 (59.0, 70.0) weeks for the ABC/DTG/3TC group (Table 15.11.1.1.1).

Adverse Events

Similar percentages of subjects in each treatment group had any AE (BVY: 234 of 282 subjects, 83.0%; ABC/DTG/3TC 239 of 281 subjects, 85.1%). The most commonly reported AEs for each treatment group were as follows:

- BVY group: upper respiratory tract infection (34 subjects, 12.1%), diarrhea (26 subjects, 9.2%), and nasopharyngitis and arthralgia (21 subjects each, 7.4%)
- ABC/DTG/3TC group: upper respiratory tract infection (32 subjects, 11.4%), headache (23 subjects, 8.2%), and nasopharyngitis and insomnia (22 subjects each, 7.8%) (Table 15.11.2.1.2.2.1)

The incidence and types of common AEs were generally similar between the 2 treatment groups throughout the randomized phase and consistent with those expected in the study population. The majority of AEs reported were Grade 1 or Grade 2 in severity. A similar percentage of subjects in each treatment group had any Grade 3 or 4 AEs (BVY: 16 subjects, 5.7%; ABC/DTG/3TC: 15 subjects, 5.3%). Adverse events considered related to study drugs were reported as follows: BVY 23 subjects, 8.2%; ABC/DTG/3TC 47 subjects, 16.7%. Overall, SAEs were reported for a similar percentage of subjects in each treatment group during the randomized phase (BVY: 17 subjects, 6.0%; ABC/DTG/3TC: 26 subjects, 9.3%). Overall, AEs that led to discontinuation of study drugs were reported as follows during the randomized phase: BVY 6 subjects, 2.1%; ABC/DTG/3TC 3 subjects, 1.1% (Table 15.11.2.1.1.1). No treatment-emergent deaths were reported in any treatment group beyond Week 48 in the randomized phase. No subjects experienced any Stage 3 opportunistic illnesses in HIV during the randomized phase (Listing 16.2.7.3).

Beyond Week 48 of the randomized phase, SAEs were reported for 2 and 4 additional subjects in the BVY and ABC/DTG/3TC groups, respectively. None of the SAEs reported beyond Week 48 in the randomized phase were considered related to study drugs and no subjects discontinued study drugs due to these SAEs (Listing 16.2.7.7).

Beyond Week 48 in the randomized phase, an AE leading to discontinuation of study drugs was reported for 1 additional subject in the ABC/DTG/3TC group. A Grade 1 AE of irritability was reported for this subject, which was considered related to study drugs (Listing 16.2.7.9).

Beyond Week 48 in the randomized phase, a full-term healthy baby was delivered for one of the subjects whose pregnancy was continuing at the time of GS-US-380-1844 Interim Week 48 CSR. In addition, 1 additional confirmed pregnancy was reported in the BVY group. The pregnancy resulted in live birth of a healthy, full term baby. No adverse pregnancy outcomes were reported (Listing 16.2.8.5).

Narratives for subjects with SAEs, who discontinued study drugs due to AEs, or became pregnant during the study are provided in Section 15.2.

Hepatic Safety

Beyond Week 48 in the randomized phase, the incidence of hepatic AEs remained comparable between the treatment groups. One subject in the ABC/DTG/3TC group had AEs of ALT, AST, and gamma-glutamyl transferase increased, which were considered related to study drug. None of the hepatic AEs resulted in discontinuation of study drugs. No additional hepatic SAEs were reported beyond Week 48 in the randomized phase. There were no clinically relevant changes from baseline for any subjects in alkaline phosphatase, ALT, AST, or total bilirubin, and the majority of abnormalities were Grade 1 or 2 (Listing 16.2.8.1.2.4 and Listing 16.2.7.5).

Any new Grade 3 or 4 ALT and/or AST abnormalities were not associated with Grade 3 or 4 abnormalities in bilirubin or alkaline phosphatase. Any additional subjects with Grade 3 or 4 abnormalities in liver-related laboratory assessments had concurrent alternative etiologies. No subject met Hy's law criteria (Listing 16.2.8.1.2.4).

Cardiovascular and Cerebrovascular Safety

Beyond Week 48 in the randomized phase, an additional Grade 3 SAE of acute coronary syndrome was reported for 1 subject in the ABC/DTG/3TC group. The event was not considered related to study drug by the investigator and did not lead to discontinuation of study drug (Listing 16.2.7.4). Narratives for all subjects with cardiovascular and cerebrovascular SAEs are provided in Section 15.2.

Bone Safety

For this final analysis, data from the Hip DXA and Spine DXA Sets collected between Week 48 and the end of the randomized phase are presented as "Post Week 48". Consistent with the data reported in the Study GS-US-380-1844 Interim Week 48 CSR, mean percentage changes from baseline in BMD at the hip or spine were similar between treatment groups at Post Week 48. Mean (SD) percentage changes from baseline in BMD at Post Week 48 were as follows:

- Hip: BVY 164 of 256 subjects (0.210% [2.6415%]); ABC/DTG/3TC 180 of 265 subjects (0.640% [2.6799%]); difference in LSM: −0.430%, 95% CI: −0.995% to 0.136%, p = 0.14) (Table 15.11.2.4.3.1 and Figure 15.11.2.4.3.2).
- Spine: BVY 162 subjects (0.651% [3.3794%]); ABC/DTG/3TC 179 subjects (0.424% [3.3580%]); difference in LSM: 0.227%, 95% CI: −0.492% to 0.945%, p = 0.54) (Table 15.11.2.4.3.3 and Figure 15.11.2.4.3.4).

There was no statistically significant difference in the categorical distribution of percentage change from baseline in hip and spine BMD between the 2 treatment groups at Post Week 48 (Tables 15.11.2.4.3.10 and 15.11.2.4.3.12).

Clinical BMD status was assessed using BMD T-scores; normal bone status was defined by a BMD T-score ≥ −1, osteopenia by a T-score from < −1 to ≥ −2.5, and osteoporosis by a T-score < −2.5. Consistent with Week 48 data, the distribution of the clinical BMD status adjusted for baseline status was similar for each treatment group at Post Week 48 at the hip and spine (Tables 15.11.2.4.3.5 and 15.11.2.4.3.6).

Renal Safety

No subject had proximal tubulopathy (including Fanconi syndrome) (Table 15.11.2.1.2.1.1) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE throughout the randomized phase (Listing 16.2.7.9).

Beyond Week 48 in the randomized phase, no new renal SAE was reported in either treatment group (Listing 16.2.7.7).

Consistent with the Week 48 data, there were no clinically relevant changes in serum creatinine and $eGFR_{CG}$ values beyond Week 48 in the randomized phase (Listing 16.2.8.1.2.3).

Laboratory Evaluations

Consistent with Week 48 data, there were no clinically relevant changes for hematology or clinical chemistry parameters (including fasting metabolic parameters) beyond Week 48 in the randomized phase (Listing 16.2.8.1.1.1 to 16.2.8.1.1.4, Listing 16.2.8.1.2.1 to 16.2.8.1.2.5, and Listing 16.2.8.1.3). The majority of subjects in both treatment groups had at least 1 laboratory abnormality (BVY: 245 subjects, 86.9%; ABC/DTG/3TC: 248 subjects, 88.3%). The majority of the laboratory abnormalities were Grade 1 or 2. Grade 3 or 4 laboratory abnormalities were reported as follows: BVY 55 subjects, 19.5%; ABC/DTG/3TC 39 subjects, 13.8%. The incidence of laboratory abnormalities was generally similar between the 2 treatment groups (Table 15.11.6.4.1.1).

There were no clinically relevant changes in vital signs parameters or body weight (Listing 16.2.8.2).

Subjects in the All BVY Analysis Set

Biktarvy was generally well tolerated in subjects who received at least 1 dose of BVY during the study. The median (Q1, Q3) duration of exposure for the All BVY group was 96.0 (48.7, 119.0) weeks (Table 15.11.1.1.2). Therefore, Week 96 was selected as the time point to evaluate renal, hematology, and clinical chemistry laboratory safety, and vital signs for the All BVY group.

Adverse Events

Cumulatively, 81.5% of subjects (446 of 547) in the All BVY group experienced an AE (Table 15.11.2.1.1.2). The majority of AEs were Grade 1 or Grade 2 in severity. The 3 most common AEs reported for subjects in the All BVY group were as follows: upper respiratory tract infection (77 subjects, 14.1%), nasopharyngitis (57 subjects, 10.4%), and diarrhea (53 subjects, 9.7%;) (Table 15.11.2.1.2.2.2). Grade 3 or 4 AEs were reported in 6.0% of subjects (33 of 547) in the All BVY group. Two subjects in the BVY group had a Grade 3 or 4 AEs considered related to study drug (Grade 4 cerebrovascular accident [1 subject]; Grade 3 suicidal ideation [1 subject with pre-existing depression, anxiety and emotional instability]) (Table 15.11.2.3.3, Listing 16.2.4.4 and Listing 16.2.7.2).

Cumulatively, 8.6% (47 subjects) in the All BVY group experienced SAEs (Table 15.11.2.1.1.2). No new SAEs considered related to study drug were reported in the OL extension phase. No subject experienced any Stage 3 opportunistic illnesses in HIV during the study (Listing 16.2.7.3).

During the OL extension phase, 1 subject died due to hypertensive heart disease, and 1 subject discontinued study drug due to a Grade 2 AE of headache. The SAE of hypertensive heart disease was not considered related to study drug and the AE of headache was considered related to study drug (Listing 16.2.7.7 and Listing 16.2.7.9).

One confirmed pregnancy was reported during the OL extension phase. The pregnancy resulted in live birth of a healthy preterm baby (gestational age: 247 days) (Listing 16.2.8.5).

Narratives for subjects with SAEs, who discontinued study drugs due to AEs, or who became pregnant during the study are provided in Section 15.2.

Hepatic Safety

Cumulatively, the overall incidence of hepatic AEs was low, 2.2% (12 of 547) of subjects who received at least 1 dose of BVY reported a hepatic AE (Table 15.11.2.4.2.1). None of the hepatic AEs resulted in discontinuation of study drugs (Listing 16.2.7.5). During the OL extension phase, 2 subjects (0.7%) in the BVY group had hepatic SAEs of acute cholecystitis and cholecystitis (1 subject each [0.4%]). Both events were Grade 2 in severity and not considered related to study drugs (Table 15.11.2.4.2.2 and Listing 16.2.7.5).

There were no clinically relevant changes from baseline in median values for alkaline phosphatase, ALT, AST, or total bilirubin (Tables 15.11.6.2.8 to 15.11.6.2.10, Table 15.11.6.2.13), and the majority of laboratory abnormalities were Grade 1 or 2 (Table 15.11.6.4.1.2). Overall in the All BVY group, Grade 3 or 4 ALT and AST abnormalities occurred in 11 of 546 subjects (2.0%) and 7 of 546 subjects (1.3%), respectively, and all were subjects randomized to receive BVY (Table 15.11.6.4.2). Grade 3 or 4 total bilirubin abnormalities occurred in 5 of 546 subjects (0.9%). No subjects experienced Grade 3 or Grade 4 alkaline phosphatase abnormalities.

Grade 3 or 4 ALT and/or AST abnormalities were not associated with Grade 3 or 4 abnormalities in bilirubin or alkaline phosphatase in all but 1 subject who experienced a Grade 2 SAE of acute hepatitis C, as described below (Listings 16.2.8.1.7 and 16.2.8.1.8). All subjects with Grade 3 or 4 abnormalities in liver-related laboratory assessments had concurrent alternative etiologies such as relevant medical history, incident hepatitis, concurrent creatine kinase elevation, incident syphilis (Listing 16.2.4.4, Table 15.11.2.1.1.2, Table 15.11.6.2.21, and Listing 16.2.8.1.2.2). No subject met Hy's law criteria (Table 15.11.6.5).

No subject had incident HIV/HBV coinfection while on study drug during the OL extension phase (Listing 16.2.8.1.9.4).

One subject in the BVY group had incident HCV infection during the OL extension phase (Listing 16.2.8.1.9.6). On Day 643, the subject experienced a Grade 2 SAE of acute hepatitis C. The event was not considered related to study drug, and the hepatic laboratory profile was consistent with underlying hepatitis infection (Listing 16.2.7.7).

Cardiovascular and Cerebrovascular Safety

Cumulatively, cardiovascular or cerebrovascular AEs were reported for 4 subjects (0.7%) in the All BVY group (Table 15.11.2.4.1.1). Cardiovascular or cerebrovascular SAEs were reported for 4 subjects (0.7%) in the All BVY group, of which 3 SAEs occurred in 2 subjects during the OL extension phase (acute myocardial infarction [1 subject], and acute coronary syndrome and

coronary artery insufficiency [both events in 1 subject]). All cardiovascular or cerebrovascular SAEs reported in the OL extension phase were not considered related to study drugs and did not result in discontinuation of study drugs (Listing 16.2.7.4).

Bone Safety

No DXA analysis was performed during the OL extension phase.

Renal Safety

No subject had proximal tubulopathy (including Fanconi syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE (Table 15.11.5). One subject in the BVY group experienced a Grade 2 SAE of acute kidney injury during the OL extension phase (Table 15.11.4.1.1.1). The event resolved and was not considered related to the study drug (Listing 16.2.7.1.1). Narrative for this subject is provided in Section 15.2.

There were no clinically relevant changes from baseline in median values for serum creatinine in the All BVY group. Median (Q1, Q3) baseline serum creatinine value in the All BVY group was 1.06 (0.94, 1.21) mg/dL. Median (Q1, Q3) change from baseline at Week 96 in the All BVY group was 0.00 (–0.08, 0.06) mg/dL (Table 15.11.6.2.23 and Figure 15.11.2.4.4.1).

Corresponding with the results for serum creatinine, there were no clinically relevant changes from baseline in the median values for $eGFR_{CG}$ in the All BVY group. Median (Q1, Q3) baseline $eGFR_{CG}$ value in the All BVY group was 97.8 (82.6, 117.6) mL/min. Median (Q1, Q3) change from baseline at Week 96 in the All BVY group was 2.4 (–5.4, 9.3) mL/min (Table 15.11.6.2.24 and Figure 15.11.2.4.4.2).

There were no clinically relevant changes from baseline in the median values for quantitative measures of albuminuria (UACR) and specific markers of proximal tubular proteinuria (urine RBP to creatinine ratio and urine beta-2-microglobulin to creatinine ratio) (Table 15.11.2.4.4.1 to 15.11.2.4.4.3, and Figure 15.11.2.4.4.3 to 15.11.2.4.4.5).

Laboratory Evaluations

There were no clinically relevant changes from baseline in the All BVY group in the median values for hematology or clinical chemistry parameters (including fasting metabolic parameters), and median values were generally within reference ranges (Table 15.11.6.1.1 to 15.11.6.3.6). Cumulatively, 476 of 546 subjects (87.2%) in the All BVY group reported at least 1 laboratory abnormality (Table 15.11.6.4.1.2). The majority of the laboratory abnormalities were Grade 1 or 2. Cumulatively, Grade 3 or 4 laboratory abnormalities were reported for 96 of 546 subjects (17.6%) in the All BVY group. The most commonly reported Grade 3 or 4 laboratory abnormality in the All BVY group was low-density lipoprotein increased (23 of 540 subjects [4.3%]) (Table 15.11.6.4.1.2).

There were no clinically relevant changes from baseline in vital signs parameters in the All BVY group (Tables 15.11.7.1.1 to 15.11.7.1.5). Median (Q1, Q3) baseline body weight value in the All BVY group was 80.7 (72.1, 92.5) kg. Median (Q1, Q3) change from baseline at Week 96 in the All BVY group was 2.3 (0.0, 5.1) kg (Table 15.11.7.2).

CONCLUSIONS:

The conclusions from this final analysis are as follows:

- Consistent with the data reported in the Week 48 CSR, high rates of virologic suppression continued to be maintained, and CD4 cell counts remained stable throughout the randomization phase in the BVY and ABC/DTG/3TC groups.
- For subjects who switched from ABC/DTG/3TC to BVY in the OL extension phase, high rates of virologic suppression continued to be maintained, and CD4 cell counts remained stable.
- There was no treatment-emergent resistance in the All BVY group and at last study visit, HIV-1 RNA < 50 copies/mL was maintained in 17 of 17 subjects with preexisting M184V/I, 3 of 3 subjects with K65R, 35 of 36 subjects with ≥ 1 TAM, and 16 of 16 subjects with a primary INSTI resistance substitution.
- Biktarvy was safe and well tolerated during the study. Common AEs were generally consistent with those expected in the subject population and the known safety profiles of study drugs.
- No subject met Hy's law criteria during the study. No subject receiving BVY had a hepatic SAE or discontinued study drugs due to hepatic AEs and no clinically relevant changes from baseline in liver-related laboratory parameters were seen.
- No clinically relevant changes from baseline in BMD at the hip or spine were seen for either treatment group at Post Week 48 of the randomized phase.
- No subject receiving BVY during the study had proximal tubulopathy (including Fanconi syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE.