FINAL WEEK 96 CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed on Regimens Containing ABC/3TC
Name of Test Drug:	Descovy® (Emtricitabine/Tenofovir Alafenamide [F/TAF])
Dose and Formulation:	Fixed-dose combination tablets of F/TAF (200/25 mg and 200/10 mg)
Indication:	Human immunodeficiency virus type 1 (HIV-1) infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-311-1717
Phase of Development:	Phase 3b
IND No.:	111851
EudraCT No.:	2015-000871-28
ClinicalTrials.gov Identifier:	NCT02469246
Study Start Date:	29 June 2015 (First Subject Screened)
Study End Date:	07 April 2017 (Last Subject Last Observation for the Primary Endpoint) 13 March 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:	23 July 2019
Previous Report Date(s):	25 August 2017

STUDY SYNOPSIS

Study GS-US-311-1717
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed on Regimens containing ABC/3TC
Investigators: This was a multicenter study.
Study Centers: Subjects were enrolled in a total of 80 study centers: 2 in Belgium, 4 in Canada, 1 in Denmark, 5 in France, 8 in Germany, 2 in Ireland, 6 in Italy, 6 in Spain, 1 in Sweden, 9 in the United Kingdom (UK), and 36 in the United States (US; including Puerto Rico).
Publications: Winston A, Post FA, DeJesus E, Podzamczer D, Di Perri G, Estrada V, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. Lancet HIV 2018 Apr;5 (4): e162-e171. Gupta SK, Post FA, Arribas JR, Jr JJE, Wohl DA, Clarke AE, et al. Renal safety of tenofovir alafenamide vs tenofovir disoproxil fumarate: A pooled analysis of 26 clinical trials. AIDS 2019. [in press]
Study Period: 29 June 2015 (First Subject Screened) 07 April 2017 (Last Subject Last Observation for the Primary Endpoint) 13 March 2019 (Last Subject Last Observation for this Report)
Phase of Development: Phase 3b
Objectives: Study GS-US-311-1717 was conducted to evaluate the efficacy, safety, and tolerability of switching abacavir (ABC)/lamivudine (3TC) to emtricitabine (F)/tenofovir alafenamide (TAF) versus maintaining ABC/3TC in virologically suppressed HIV-1 infected subjects. The primary objective of this study was as follows: • To evaluate the efficacy of switching ABC/3TC to F/TAF versus maintaining ABC/3TC in HIV-1 infected subjects who are virologically suppressed on regimens containing ABC/3TC 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 efficacy, safety, and tolerability of 2 regimens through Week 48 and Week 96 • To evaluate the bone safety of 2 regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48 and Week 96

Methodology: This was a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of switching ABC/3TC to F/TAF fixed-dose combination (FDC) tablet versus continuing ABC/3TC in HIV-1 infected subjects who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing ABC/3TC for ≥ 6 consecutive months prior to screening.

All eligible subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

- **Treatment Group 1: (F/TAF+3rd Agent group):** F/TAF + placebo-to-match ABC/3TC; third antiretroviral (ARV) agent remained the same (planned N = 250); a TAF dose of 10 or 25 mg was administered based on the general recommendation that F/TAF 200/10 mg should be used with boosted third agents and F/TAF 200/25 mg should be used with unboosted third agents
- **Treatment Group 2: (ABC/3TC+3rd Agent group):** ABC/3TC + placebo-to-match F/TAF; third ARV agent remained the same (planned N = 250)

Randomization was stratified by the third agent (boosted protease inhibitor [PI] vs any other protocol-allowed third agent) in a subject's existing regimen.

Following the screening and Day 1 visits, subjects returned for study visits at Weeks 4, 8, and 12, and then every 12 weeks through Week 96. After Week 96, all subjects continued to take their blinded study drug and attend visits every 12 weeks until treatment assignments were unblinded, at which point subjects returned for an unblinding visit. After unblinding, in countries where F/TAF FDC was not commercially available, subjects were given the option to receive the open-label F/TAF FDC and attend study visits every 12 weeks until it became commercially available (except in certain countries such as the UK), or until Gilead terminated the study in that country. Subjects who completed the study through the unblinding visit and did not wish to continue to receive open-label F/TAF FDC were required to return to the clinic 30 days after study drug completion for a 30-day follow-up visit.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 500 subjects (approximately 250 subjects in each of Treatment Group 1 and Treatment Group 2)
Analyzed: 567 subjects

Subjects n (%)	F/TAF	ABC/3TC	Total
Randomized	285	282	567
Safety Analysis Set	280 (98.2%)	276 (97.9%)	556 (98.1%)
Full Analysis Set (FAS)	280 (98.2%)	276 (97.9%)	556 (98.1%)
Week 96 Per Protocol (PP) Analysis Set	230 (80.7%)	239 (84.8%)	469 (82.7%)
Hip DXA Analysis Set	253 (88.8%)	248 (87.9%)	501 (88.4%)
Spine DXA Analysis Set	256 (89.8%)	251 (89.0%)	507 (89.4%)
Open-Label F/TAF Analysis Set	6 (2.1%)	5 (1.8%)	11 (1.9%)

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: Subjects enrolled in this study were HIV-1 positive adults receiving an ARV regimen containing ABC/3TC in combination with a protocol-allowed third agent who had maintained plasma HIV-1 RNA < 50 copies/mL for ≥ 6 consecutive months prior to the screening visit. Subjects were also required to have HIV-1 RNA < 50 copies/mL at the screening visit and an estimated glomerular filtration rate (eGFR) as calculated by the Cockcroft-Gault method ($eGFR_{CG}$) ≥ 50 mL/min at screening.

Duration of Treatment: Subjects received blinded study drug for at least 96 weeks. After Week 96, all subjects continued to take their blinded study drug and attended visits every 12 weeks until treatment assignments were unblinded, at which point all subjects returned for an unblinding visit. After unblinding, in countries where F/TAF FDC was not commercially available, subjects were given the option to receive the open-label F/TAF FDC and attend study visits every 12 weeks until it became commercially available (except in certain countries such as the UK), or until Gilead terminated the study in that country.

Test Product, Dose, Mode of Administration, and Batch No.:
F/TAF tablet (200/10 mg, 200/25 mg, or placebo-to-match) administered orally in combination with a third ARV agent, once daily at approximately the same time each day.

F/TAF 200/10 mg Batch Numbers:

- CR1411B1, CR1503B1, and CR1508B1

F/TAF 200/10 mg Placebo-to-Match Batch Numbers:

- CR1312B1 and CR1510B1

F/TAF 200/25 mg Batch Numbers:

- CR1412B1, CR1509B1, CR1604B1, and CR1606B1

F/TAF 200/25 mg Placebo-to-Match Batch Numbers:

- CR1311B1, CR1507B2, and CR1608B1

Reference Therapy, Dose, Mode of Administration, and Batch No.:
ABC/3TC tablet (600/300 mg or placebo-to-match) administered orally in combination with a third ARV agent, once daily at approximately the same time each day.

ABC/3TC 600/300 mg Batch Numbers:

- 4ZP7400, 5ZP8170, 5ZP8362, 5ZP0276, 5ZP0504, 6ZP5909, 6ZP5669, and 7ZP7424

ABC/3TC 600/300 mg Placebo-to-Match Batch Numbers:

- EP1501B1 and EP1502B1

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 US Food and Drug Administration (FDA)-defined snapshot algorithm.

Secondary efficacy endpoints evaluated were as follows:

- The proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Weeks 48 and 96 using the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 using the US FDA-defined snapshot algorithm
- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Weeks 48 and 96 using the US FDA-defined snapshot algorithm
- The change from baseline in CD4 cell count at Weeks 48 and 96

Tertiary efficacy endpoints evaluated were as follows:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 48 and 96 as defined by 2 different missing data imputation methods (missing = failure [M = F] and missing = excluded [M = E])
- The change from baseline in CD4% at Weeks 48 and 96

Pharmacokinetics/Pharmacodynamics: No pharmacokinetic (PK) or pharmacodynamic (PD) assessments were performed for this report.

Safety: Baseline and postbaseline safety assessments included adverse events (AEs), BMD using dual-energy x-ray absorptiometry (DXA), physical examinations, 12-lead electrocardiograms (ECGs), vital signs, weight, and clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy testing) including bone biomarkers (type I collagen C-telopeptide [CTx], procollagen type I N-terminal propeptide [P1NP]), renal safety analyses (serum creatinine, $eGFR_{CG}$, and eGFR calculated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine method [$eGFR_{CKD\text{-}EPI,\ creatinine}$]), proteinuria by urinalysis and quantitative assessment (urine protein to creatinine ratio, [UPCR]), and renal biomarkers (urine retinol binding protein [RBP] to creatinine ratio and urine beta-2-microglobulin to creatinine ratio).

Statistical Methods:

Efficacy: In the interim Week 48 analysis, efficacy endpoints at Week 48 were assessed using the FAS, which included all subjects who were randomized and received at least 1 dose of study drug by 23 May 2016 (n = 501). In this final analysis, efficacy endpoints at Week 48 were repeated using the finalized data including 556 subjects in the FAS, who were randomized and received at least 1 dose of study drug, to confirm results observed in the interim Week 48 analysis.

For the primary efficacy endpoint (proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm), noninferiority was assessed using a 2-sided exact 95% CI approach, with a noninferiority margin of 10%. A significance level of 0.04998 was used (corresponding to 95.002% CI) to account for 2 interim Independent Data Monitoring Committee (IDMC) analyses performed prior to the interim Week 48 analysis. It was concluded that switching to F/TAF would be noninferior to maintaining ABC/3TC if the lower bound of the 2-sided 95.002% CI of the difference (F/TAF+3rd Agent group − ABC/3TC+3rd Agent group) in the response rate was greater than −10%.

If noninferiority of F/TAF+3rd Agent versus ABC/3TC+3rd Agent was established, the same 95.002% CI used in evaluating noninferiority at Week 48 was used to evaluate superiority. If the lower bound of the 95.002% CI was greater than 0, superiority of F/TAF+3rd Agent over ABC/3TC+3rd Agent was established. The 2-sided Fisher exact test was also used to assess superiority as a secondary assessment.

The proportions of subjects with HIV-1 RNA < 50 copies/mL at Week 96 and < 20 copies/mL at Weeks 48 and 96 as determined by the US FDA-defined snapshot algorithm were analyzed using the same method as for the primary endpoint based on the FAS for the endpoints at Week 48 and both FAS and Week 96 Per Protocol (PP) Analysis Set for the endpoints at Week 96, except that CIs were constructed at the 95% level.

The proportions of subjects with HIV-1 RNA $\underline{\geq}$ 50 copies/mL at Weeks 48 and 96 were analyzed using the same method as described for the primary endpoint, except that CIs were constructed at a 95% level for the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 96. Noninferiority of treatment with F/TAF+3rd Agent relative to treatment with ABC/3TC+3rd Agent was assessed based on the exact CI for the failure rates, with a noninferiority margin of 4%.

The number and percentage of subjects with HIV-1 RNA < 50 copies/mL (M = F [missing = failure] and M = E [missing = excluded] methods) and change from baseline in CD4 cell count were summarized by visit throughout the double-blind phase for the FAS and Week 96 PP Analysis Sets using descriptive statistics. CD4% was similarly analyzed using the FAS. The number and percentage of subjects with HIV-1 RNA < 50 copies/mL and the change from baseline in CD4 cell counts were summarized by visit through the open-label phase for the Open-Label F/TAF Analysis Set using descriptive statistics.

Pharmacokinetics/Pharmacodynamics: No PK or PD assessments were performed for this report.

Safety: The Safety Analysis Set included all randomized subjects who received ≥ 1 dose of study drug. Safety data were summarized by treatment group using descriptive statistics.

Percentage changes from baseline in hip BMD and spine BMD, were 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 postbaseline visit using analysis of variance, which included third agent randomization stratum and treatment as fixed effects.

SUMMARY OF RESULTS:

Subject Disposition and Demographics: Of the 626 subjects screened, 567 were randomized, and 556 received at least 1 dose of study drug (F/TAF+3rd Agent, 280 subjects; ABC/3TC+3rd Agent, 276 subjects). Eleven randomized subjects (F/TAF+3rd Agent, 5 subjects; ABC/3TC+3rd Agent, 6 subjects) did not receive study drug due to withdrawal of consent, protocol violation, loss to follow-up, or discontinuation from the study per investigator's discretion.

Of the 556 subjects treated with study drug in the double-blind phase, 22.3% (124 subjects) discontinued study drug (F/TAF+3rd Agent, 24.6%, 69 subjects; ABC/3TC+3rd Agent, 19.9%, 55 subjects) and 20.1% (112 subjects) prematurely discontinued from the study (F/TAF+3rd Agent, 22.1%, 62 subjects; ABC/3TC+3rd Agent, 18.1%, 50 subjects) in the double-blind phase. The most common reasons subjects prematurely discontinued study drug were withdrawal of

consent (F/TAF+3rd Agent, 9.3%, 26 subjects; ABC/3TC+3rd Agent, 8.3%, 23 subjects), AE (F/TAF+3rd Agent, 6.1%, 17 subjects; ABC/3TC+3rd Agent, 5.1%, 14 subjects), and investigator's discretion (F/TAF+3rd Agent, 3.6%, 10 subjects; ABC/3TC+3rd Agent, 3.6%, 10 subjects).

Eleven subjects entered the open-label phase (6 subjects initially randomized to F/TAF+3rd Agent; 5 subjects initially randomized to ABC/3TC+3rd Agent) and were treated with F/TAF+3rd Agent. All 11 subjects completed the study drug and study in the open-label phase.Demographic and baseline characteristics were similar between the 2 treatment groups. Most subjects in the Safety Analysis Set were male (81.8%), with a median age of 52 years (range: 20 to 79 years); most were white (72.7%) or black (23.4%) and most were Not Hispanic or Latino (93.7%). The median (Q1, Q3) body mass index (BMI) was 26.0 (23.7, 29.4) kg/m^2.

Baseline disease characteristics were similar between the 2 treatment groups. The study enrolled a virologically suppressed, HIV-infected population; thus, 99.1% of subjects in the Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL. The median (Q1, Q3) baseline CD4 cell count was 671 (509, 874) cells/µL (F/TAF+3rd Agent, 654 [489, 849] cells/µL; ABC/3TC+3rd Agent, 700 [546, 891] cells/µL), with approximately three-quarters (76.4%) of subjects having a baseline CD4 count ≥ 500 cells/µL. The median (Q1, Q3) baseline CD4% was 34.2% (28.1%, 40.5%). The most common HIV risk factor category was homosexual sex (62.2% of subjects); 30.9% of subjects reported heterosexual sex as the mode of infection. The median (Q1, Q3) $eGFR_{CG}$ at baseline was 100.8 (82.3, 120.2) mL/min.

Randomization was stratified by the third agent (boosted PI vs others) in a subject's existing regimen. The distributions of third agents were similar in the 2 treatment groups (boosted PI: F/TAF+3rd Agent, 30.0%, 84 subjects; ABC/3TC+3rd Agent, 30.1%, 83 subjects; others: F/TAF+3rd Agent, 70.0%, 196 subjects; ABC/3TC+3rd Agent, 69.9%, 193 subjects). Values for eGFR were similar in the 2 treatment groups.

Efficacy Results: Percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were as follows: F/TAF+3rd Agent, 88.6%; ABC/3TC+3rd Agent, 92.4%; difference in percentages: −3.8%, 95.002% CI: −8.9% to 1.1%. Because the lower bound of the 2-sided 95.002% CI of the difference between treatment groups (F/TAF+3rd Agent − ABC/3TC+3rd Agent) was greater than the prespecified −10% margin, switching to F/TAF was determined to be noninferior to maintaining ABC/3TC.

Using the US FDA-defined snapshot algorithm, the percentage of subjects in the FAS with HIV-1 RNA < 50 copies/mL at Week 96 in the F/TAF+3rd Agent group was lower than that in the ABC/3TC+3rd Agent group (F/TAF+3rd Agent, 82.1%; ABC/3TC+3rd Agent, 88.4%; difference in percentages: −6.3%, 95% CI: −12.3% to −0.3%). This may be explained by a greater proportion of subjects in the F/TAF group than in the ABC/3TC group having discontinued for reasons other than virologic failure before Week 96 (F/TAF+3rd Agent, 42 subjects; ABC/3TC+3rd Agent, 28 subjects) or lacking Week 96 data (F/TAF+3rd Agent, 1 subject; ABC/3TC+3rd Agent, 1 subject) (15.4% compared with 10.5%). When the analysis was performed using the Week 96 PP Analysis Set, the percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 96 were similar for each treatment group (F/TAF+3rd Agent, 98.7%; ABC/3TC+3rd Agent, 99.2%; difference in percentages: −0.5%, 95% CI: −3.1% to 1.9%).

Percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 as determined by the US FDA-defined snapshot algorithm were as follows: F/TAF+3rd Agent, 1.8%; ABC/3TC+3rd Agent, 0.7%; difference in percentages: 1.1%, 95.002% CI: −1.0% to 3.5%.

Percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 96 as determined by the US FDA-defined snapshot algorithm were as follows: F/TAF+3rd Agent, 2.5%; ABC/3TC+3rd Agent, 1.1%; difference in percentages: 1.4%, 95% CI: −1.0% to 4.2%. Percentages of subjects in the Week 96 PP Analysis Set with HIV-1 RNA ≥ 50 copies/mL at Week 96 were similar for each treatment group (F/TAF+3rd Agent, 1.3%; ABC/3TC+3rd Agent, 0.8%; difference in percentages: 0.5%, 95% CI: −1.9% to 3.1%).

Percentages of subjects in the FAS with HIV-1 RNA < 20 copies/mL using the US FDA-defined snapshot algorithm were similar in each treatment group at Week 48 (F/TAF+3rd Agent, 85.7%; ABC/3TC+3rd Agent, 87.3%; difference in percentages: −1.6%, 95% CI: −7.4% to 4.2%) and Week 96 (F/TAF+3rd Agent, 80.4%; ABC/3TC+3rd Agent, 86.2%; difference in percentages: −5.9%, 95% CI: −12.2% to 0.4%).

Similar percentages of subjects maintained HIV-1 RNA < 50 copies/mL in each treatment group as assessed using the M = F and M = E methods at Week 48 for the FAS.

- **M = F:** F/TAF+3rd Agent, 91.4%; ABC/3TC+3rd Agent, 93.8%; difference in percentages: −2.4%, 95% CI: −7.0% to 2.0%
- **M = E:** F/TAF+3rd Agent, 99.2%; ABC/3TC+3rd Agent, 99.6%; difference in percentages: −0.4%, 95% CI: −2.5% to 1.5%

As assessed using the M = F method at Week 96 for the FAS, the percentage of subjects who maintained HIV-1 RNA < 50 copies/mL in the F/TAF+3rd Agent group was lower than that in the ABC/3TC+3rd Agent group. However, similar percentages of subjects maintained HIV-1 RNA < 50 copies/mL in each treatment group as assessed using the M = E method at Week 96 for the FAS. This may be due to the greater proportion of subjects in the F/TAF group than in the ABC/3TC group having discontinued for reasons other than virologic failure before Week 96.

- **M = F:** F/TAF+3rd Agent, 85.0%; ABC/3TC+3rd Agent, 91.7%; difference in percentages: −6.7%, 95% CI: −12.2% to −1.1%
- **M = E:** F/TAF+3rd Agent, 98.8%; ABC/3TC+3rd Agent, 99.2%; difference in percentages: −0.5%, 95% CI: −3.0% to 1.8%

Percentages of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS were similar between the 2 treatment groups for most of the subgroups analyzed (age, race, third agent, region, and study drug adherence) and for the subgroups of female and Hispanic/Latino subjects; however, in the subgroups of male and Not Hispanic/Latino subjects, there was a lower percentage of subjects with HIV-1 RNA < 50 copies/mL in the F/TAF group compared with the ABC/3TC group.

This may be explained by the greater number of male subjects in the F/TAF+3rd Agent group compared with the ABC/3TC+3rd Agent group who did not have an on-treatment HIV-1 RNA value recorded in the Week 96 analysis window due to reasons other than virologic failure (F/TAF+3rd Agent, 15.4%; ABC/3TC+3rd Agent, 8.8%), and the greater number of Not Hispanic/Latino subjects in the F/TAF+3rd Agent group who did not have an on-treatment

HIV-1 RNA value recorded in the Week 96 analysis window due to reasons other than virologic failure (F/TAF+3rd Agent, 15.2%; ABC/3TC+3rd Agent, 10.1%).

Mean (SD) baseline CD4 cell counts were similar between treatment groups (F/TAF+3rd Agent, 703 [298.7] cells/μL; ABC/3TC+3rd Agent, 727 [275.2] cells/μL). CD4 cell counts were maintained for both treatment groups, with mean (SD) changes from baseline for the FAS, based on observed data, as follows:

- **Week 48:** F/TAF+3rd Agent, −30 (152.3) cells/μL; ABC/3TC+3rd Agent, 2 (171.2) cells/μL; difference in least-squares means (LSM): −32 cells/μL, 95% CI: −61 to −4 cells/μL; p = 0.026
- **Week 96:** F/TAF+3rd Agent, −29 (160.7) cells/μL; ABC/3TC+3rd Agent, 10 (178.2) cells/μL; difference in LSM: −39 cells/μL, 95% CI: −70 to −8 cells/μL; p = 0.013

Observed differences between the 2 treatment groups were not considered clinically relevant.

Mean (SD) baseline CD4% was similar for each treatment group. Mean (SD) changes from baseline in CD4% at Weeks 48 and 96 were as follows:

- **Week 48:** F/TAF+3rd Agent, 0.7% (3.72%); ABC/3TC+3rd Agent, −0.1% (3.29%); difference in LSM: 0.8%, 95% CI: 0.1% to 1.4%
- **Week 96:** F/TAF+3rd Agent, 1.3% (4.29%); ABC/3TC+3rd Agent, 0.7% (3.55%); difference in LSM: 0.7%, 95% CI: 0.0% to 1.4%

Resistance development through Week 96/EOS was rare in both treatment groups. In the F/TAF+3rd Agent group, 4 of 280 subjects (1.4%) developed resistance mutations to study drug. One subject developed the K65K/R resistance mutation, 2 subjects developed the M184V/I mutation, and 1 subject developed the NNRTI mutation K103N while on third agent NVP. In the ABC/3TC+3rd Agent group, 1 of 276 subjects (0.4%) developed resistance to their third agent; ATV (M46I, I50L, and N88S).

Pharmacokinetics/Pharmacodynamics Results: No PK or PD assessments were performed for this report.

Safety Results: In subjects switching from their baseline regimen, F/TAF+3rd Agent was generally well tolerated through a median of 124.3 weeks of exposure, as evidenced by the infrequent discontinuations due to AEs and study drug-related SAEs. In subjects who stayed on their baseline regimen, study drug was generally well tolerated through a median of 127.1 weeks of exposure.

Adverse Events

Similar percentages of subjects in each treatment group had any AE reported (F/TAF+3rd Agent, 91.1%, 255 of 280 subjects; ABC/3TC+3rd Agent, 93.8%, 259 of 276 subjects), or an SAE (F/TAF+3rd Agent, 19.6%, 55 subjects; ABC/3TC+3rd Agent, 11.6%, 32 subjects) during the double-blind phase. The incidence of SAEs considered related to study drug was low in each treatment group (F/TAF+3rd Agent, 0.7%, 2 subjects; ABC/3TC+3rd Agent, 0.4%, 1 subject).

Few subjects in either group discontinued study drug due to an AE (F/TAF+3rd Agent, 6.1%, 17 subjects; ABC/3TC+3rd Agent, 5.1%, 14 subjects). Nausea leading to study drug discontinuation was reported for 2 subjects in the F/TAF+3rd Agent group. Depression and

pruritus leading to study drug discontinuation were reported for 2 subjects each in the ABC/3TC+3rd Agent group. No other AE that led to study drug discontinuation was reported for more than 1 subject in either group. No pregnancies were reported during the study.

During the double-blind phase, 4 treatment-emergent deaths were reported in the F/TAF+3rd Agent group, 1 due to sudden cardiac death, 1 due to myocardial infarction, 1 due to cardiorespiratory arrest, and 1 due to unknown cause. None of these deaths was considered related to study drug.

Common AEs were consistent with those expected in the study population, the known safety profiles of the study drugs, and previous clinical study experience with FTC+TAF in combination with EVG+COBI administered as E/C/F/TAF (Genvoya). The most common AEs by treatment group were as follows:

- **F/TAF+3rd Agent:** nasopharyngitis (20.4%, 57 subjects), upper respiratory tract infection (12.9%, 36 subjects), and cough (12.1%, 34 subjects)
- **ABC/3TC+3rd Agent:** nasopharyngitis (17.8%, 49 subjects), upper respiratory tract infection (16.7%, 46 subjects), and diarrhea (13.4%, 37 subjects)

Overall, the rates and types of AEs observed in this study were similar in the 2 groups.

Bone Safety

Similar percentages of subjects in each group had a treatment-emergent fracture event (F/TAF+3rd Agent, 1.1%, 3 subjects; ABC/3TC+3rd Agent, 1.4%, 4 subjects; p = 0.72). All reported fracture events were considered unrelated to study drug by the investigator and none resulted in discontinuation of study drug.

There were minimal increases from baseline in mean (SD) BMD in both the hip and spine in both treatment groups in the double-blind phase. Mean (SD) percentage changes from baseline in BMD at Week 96 (observed data) were as follows (F/TAF+3rd Agent group vs ABC/3TC+3rd Agent group):

- **Hip:** 0.169% (2.7277) vs 0.021% (2.7212); p = 0.53
- **Spine:** 0.178% (3.8881) vs 0.235% (4.3066); p = 0.89

The categorical distribution of percentage change from baseline in hip and spine BMD was similar in the 2 treatment groups at Weeks 48 and 96.

Bone turnover remained stable and was similar for each treatment group at Weeks 48 and 96 with minimal changes from baseline in serum levels of the bone formation biomarker P1NP and the bone resorption biomarker CTx in both treatment groups.

Renal Safety

In the F/TAF+3rd Agent group, 1 subject had an SAE of acute kidney injury not considered related to study drug and leading to discontinuation of study drug; 2 additional subjects had SAEs of acute kidney injury that were not considered related to study drug by the investigator and did not lead to discontinuation of study drug; 1 subject had an SAE of nephrolithiasis that was not considered related to study drug by the investigator and did not lead to discontinuation of study drug; 1 subject had an SAE of renal colic considered related to study drug that did not

lead to study drug discontinuation. Additionally, 1 subject had a nonserious AE of blood creatinine increased considered related to study drug that led to study drug discontinuation.

In the ABC/3TC+3rd Agent group no subject had a renal AE that was considered serious or resulted in discontinuation of study drug, and no cases of proximal renal tubulopathy (including Fanconi syndrome) were reported in either treatment group during the study.

There were no changes from baseline in serum creatinine through Weeks 48 and 96 in both treatment groups in the double-blind phase. At Week 96, mean (SD) changes from baseline in serum creatinine were as follows: F/TAF+3rd Agent, 0.01 (0.126) mg/dL; ABC/3TC+3rd Agent, 0.01 (0.126) mg/dL; p = 0.84.

For subjects who switched to F/TAF+3rd Agent, there were minimal increases from baseline in $eGFR_{CG}$ values at Week 4 of the double-blind phase, which remained stable through Week 96, compared with minimal decreases from baseline among subjects who remained on an ABC/3TC+3rd Agent regimen. Median changes from baseline at Week 96 were as follows: F/TAF+3rd Agent, 0.6 mL/min; ABC/3TC+3rd Agent, −2.4 mL/min; p = 0.090. Median changes from baseline at Week 96 in $eGFR_{CKD\text{-}EPI,\ creatinine}$ were as follows: F/TAF+3rd Agent, −1.5 mL/min; ABC/3TC+3rd Agent, −1.3 mL/min; p = 0.86. None of these changes was clinically relevant.

At Week 96, among subjects with nonmissing values, a similar percentage of subjects in each treatment group showed a worsening from baseline in proteinuria toxicity grade (F/TAF+3rd Agent, 6.2%, 14 of 227 subjects; ABC/3TC+3rd Agent, 9.1%, 22 of 242 subjects). A higher percentage of subjects in the F/TAF+3rd Agent group showed an improvement from baseline in proteinuria toxicity grade (F/TAF+3rd Agent, 71.4%, 15 of 21 subjects; ABC/3TC+3rd Agent, 52.0%, 13 of 25 subjects). The shift of proteinuria toxicity grading adjusted for baseline toxicity grading did not show a statistically significant difference between treatment groups at Week 96 (p = 0.086). Grade 1 or 2 proteinuria was reported as an AE in 1 subject in the F/TAF+3rd Agent group and in 2 subjects in the ABC/3TC+3rd Agent group.

There were no clinically relevant increases from baseline in mean urine RBP to creatinine or urine beta-2-microglobulin to creatinine ratios through Week 96 in either treatment group in the double-blind phase. There were no differences between treatment groups.

Laboratory Abnormalities

There were no clinically relevant changes from baseline, or differences between treatment groups in median values for hematology and clinical chemistry parameters during the double-blind phase. With the exception of lipase, which was measured only for subjects with elevated amylase, median values were within normal ranges throughout the study.

Most subjects in each treatment group in the double-blind phase had at least 1 laboratory abnormality reported during the study (F/TAF+3rd Agent, 94.3%, 263 subjects; ABC/3TC+3rd Agent, 96.0%, 264 subjects); most reported abnormalities were Grade 1 or Grade 2. The incidence of laboratory abnormalities of any grade were balanced across treatment groups for most chemistry, hematology, and urinalysis parameters. Similar percentages of subjects in the F/TAF+3rd Agent group and the ABC/3TC+3rd Agent group had Grade 3 or 4 abnormalities (F/TAF+3rd Agent, 30.5%, 85 subjects; ABC/3TC+3rd Agent, 25.8%, 71 subjects).

Metabolic Laboratory Parameters

There were minimal changes in fasting values of total cholesterol, LDL cholesterol, HDL cholesterol, total cholesterol to HDL ratio, triglycerides, and glucose for either treatment group.

Median (Q1, Q3) changes from baseline at Week 96 for the F/TAF+3rd Agent group compared with ABC/3TC+3rd Agent group were as follows: total cholesterol −2 (−20, 20) mg/dL vs −1 (−19, 18) mg/dL; LDL cholesterol 2 (−15, 20) mg/dL vs 1 (−15, 16) mg/dL; HDL cholesterol −2 (−7, 5) mg/dL vs 0 (−5, 6) mg/dL; total cholesterol to HDL ratio 0.1 (−0.4, 0.4) vs 0.0 (−0.5, 0.4); triglycerides −1 (−33, 28) mg/dL vs 0 (−37, 26) mg/dL; and glucose 2 (−6, 9) mg/dL vs 3 (−4, 10) mg/dL. None of the changes was considered clinically relevant.

There were no clinically relevant findings in other safety-related assessments.

CONCLUSIONS:

- In virologically suppressed, HIV-1 infected subjects, virologic suppression (HIV-1 RNA < 50 copies/mL) remained high at Week 48 in both subjects who had switched to F/TAF and subjects who had maintained their ABC/3TC-containing regimen, using the FAS (F/TAF+3rd Agent, 88.6%; ABC/3TC+3rd Agent, 92.4%; difference in percentages: −3.8%, 95.002% CI: −8.9% to 1.1%). Switching to F/TAF was noninferior to maintaining ABC/3TC.
- Virologic suppression (HIV-1 RNA < 50 copies/mL) remained high at Week 96 (F/TAF+3rd Agent, 82.1%; ABC/3TC+3rd Agent, 88.4%; difference in percentages: −6.3%, 95% CI: −12.3% to −0.3%).
- CD4 cell counts and CD4 percentage were maintained in each group.
- Resistance development through Week 96/EOS was rare in both treatment groups. In the F/TAF+3rd Agent group, 4 of 280 subjects (1.4%) developed resistance mutations to study drug, and in the ABC/3TC+3rd Agent group, 1 of 276 subjects (0.4%) developed resistance to their third agent.
- In both treatment groups, study drugs were well tolerated, with low rates of study drug-related SAEs and AEs leading to study drug discontinuation. Common AEs were generally consistent with those expected in the subject population and the known safety profiles of the study drugs.
- Renal laboratory parameters, spine and hip BMD did not change upon switching from ABC/3TC to F/TAF.
- There were no clinically relevant changes in lipids upon switching from ABC/3TC to F/TAF.