FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed on Regimens containing FTC/TDF
Name of Test Drug:	Emtricitabine/Tenofovir Alafenamide (F/TAF; Descovy®)
Dose and Formulation:	Fixed-dose combination tablet 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-311-1089
Phase of Development:	Phase 3
IND No.:	111851
EudraCT No.:	2013-005138-39
ClinicalTrials.gov Identifier:	NCT02121795
Study Start Date:	28 February 2014 (First Subject Screened)
Study End Date:	12 August 2015 (Last Subject Observation for the Primary Endpoint) 01 March 2019 (Last Subject Observation for this Report)
Principal or Coordinating Investigator:	Name: PPD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	22 August 2019
Previous Report Date(s):	14 November 2016 (Week 96 Interim Report) 13 November 2015 (Week 48 Interim Report)

STUDY SYNOPSIS

Study GS-US-311-1089

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

Title of Study: A Phase 3, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed on Regimens Containing FTC/TDF

Investigators: This was a multicenter study

Study Centers: Subjects were enrolled at a total of 78 study sites: 1 in Belgium, 4 in Canada, 5 in France, 2 in Italy, 6 in the United Kingdom, and 60 in the United States.

Publications: Gallant JE, Daar ES, Raffi F, Brinson C, Ruane P, DeJesus E, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. Lancet HIV 2016;3(4):e158-e165.

Study Period:

28 February 2014 (First Subject Screened)
12 August 2015 (Last Subject Observation for the Primary Endpoint)
01 March 2019 (Last Subject Observation for this Report)

Phase of Development: Phase 3

Objectives:

Study GS-US-311-1089 was conducted to evaluate the efficacy, safety, and tolerability of switching emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) to emtricitabine (F)/tenofovir alafenamide (TAF) versus maintaining FTC/TDF in virologically suppressed HIV-1 infected subjects.

The primary objective of this study was as follows:

- To evaluate the efficacy of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in HIV-1 positive subjects who were virologically suppressed on regimens containing FTC/TDF 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 bone safety of 2 regimens as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) at Week 48
- To evaluate the efficacy, safety, and tolerability of 2 regimens through Week 48 and Week 96
- To evaluate the pharmacokinetics (PK) of TAF and tenofovir (TFV)

Methodology:

This was a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of switching FTC/TDF to F/TAF versus continuing FTC/TDF in HIV-1 positive subjects who had been virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen containing FTC/TDF and a protocol-allowed antiretroviral (ARV) third agent 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 FTC/TDF; third ARV agent remained the same (planned n 330); a TAF dose of 10 or 25 mg was administered, based on the general recommendation that F/TAF 200/25 mg should be used with unboosted third agents and F/TAF 200/10 mg should be used with boosted third agents
- **Treatment Group 2 (FTC/TDF+3rd Agent group):**
- FTC/TDF + placebo-to-match F/TAF; third ARV agent remained the same (planned n 330)

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 attended visits every 12 weeks until treatment assignments were unblinded, at which point all subjects returned for an unblinding visit and were given the option to receive open-label (OL) F/TAF and attend visits every 12 weeks until F/TAF was commercially available or until Gilead Sciences terminated the F/TAF clinical development program. Subjects who completed the study through the unblinding visit and did not wish to receive OL F/TAF were required to return to the clinic 30 days after completion of study drug for a 30-Day Follow-up Visit.

Number of Subjects (Planned and Analyzed):

Planned: 660 subjects (330 subjects in each of Treatment Group 1 and Treatment Group 2)

Analyzed (by analysis set):

Randomized Analysis Set

Subjects n (%)	F/TAF + 3rd Agent	FTC/TDF + 3rd Agent	Total
Randomized	334	334	668
Safety Analysis Set	333 (99.7%)	330 (98.8%)	663 (99.3%)
Full Analysis Set	333 (99.7%)	330 (98.8%)	663 (99.3%)
Hip DXA Analysis Set	321 (96.1%)	317 (94.9%)	638 (95.5%)
Spine DXA Analysis Set	321 (96.1%)	320 (95.8%)	641 (96.0%)

DXA dual energy x ray absorptiometry
The denominator for percentages is the number of subjects in the Randomized Analysis Set.

All F/TAF Analysis Set

Subjects n (%)	F/ TAF + 3rd Agent	FTC/TDF + 3rd Agent →F/TAF + 3rd Agent	All F/TAF + 3rd Agent
Subjects in All F/TAF Analysis Set	333	31	364
Subjects in All F/TAF Hip DXA Analysis Set	321 (96.4%)	29 (93.5%)	350 (96.2%)
Subjects in All F/TAF Spine DXA Analysis Set	321 (96.4%)	30 (96.8%)	351 (96.4%)

DXA dual energy x ray absorptiometry
The denominator for percentages is the number of subjects in the All F/TAF Analysis Set.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were HIV-1 positive adults receiving an ARV regimen containing FTC/TDF 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 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 and were given the option to receive OL F/TAF and attend visits every 12 weeks until F/TAF was commercially available, or until Gilead Sciences terminated the F/TAF clinical development program.

Test Product, Dose, Mode of Administration, and Lot 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 in the morning at approximately the same time each day.

F/TAF 200/10 mg Lot Numbers: CR1308B1, CR1407B1, CR1411B1, and CR1508B1

F/TAF 200/10 mg Placebo-to-Match Lot Number: CR1312B1

F/TAF 200/25 mg Lot Numbers: CR1305B1, CR1408B1, CR1412B1, and CR1504B1

F/TAF 200/25 Placebo-to-Match Lot Number: CR1311B1 and CR1507B1

Reference Therapy, Dose, Mode of Administration, and Lot No.:

FTC/TDF tablet (200/300 mg or placebo-to-match) administered orally in combination with a third ARV agent, once daily in the morning at approximately the same time each day

FTC/TDF 200/300 mg Lot Numbers: V1206B1, V1207B1, and V1501B1

FTC/TDF 200/300 mg Placebo-to-Match Lot Number: V1107B1 and V1502B1

Criteria for Evaluation:

Efficacy:

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

The secondary efficacy endpoints included:

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

Pharmacokinetics:

Sparse sampling was performed through Week 48 for the analysis of TAF and TFV plasma concentrations. The results of these analyses were presented in a separate population PK report. Trough blood samples were collected at Week 4 to determine TFV-diphosphate in peripheral blood mononuclear cells; the results of these analyses were presented in the Week 48 clinical study report (CSR). No additional PK data were collected after Week 48.

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], and parathyroid hormone [PTH]), renal safety analyses (serum creatinine, $eGFR_{CG}$, and eGFR calculated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine method [$eGFR_{CKD\ EPI,\ creatinine}$], proteinuria by urinalysis and quantitative assessment [urine protein to creatinine ratio (UPCR), and urine albumin to creatinine ratio]), and renal biomarkers (urine retinol binding protein to creatinine ratio and urine beta-2-microglobulin to creatinine ratio).

Patient-Reported Outcomes:

Medical Outcome Study Short Form-36 (SF-36) and EQ-5D-3L questionnaires were administered at Day 1, Week 24, and every 24 weeks thereafter, and at the Early Study Drug Discontinuation Visit. A health utilization assessment was conducted on Day 1 and at every postbaseline visit.

Statistical Methods:

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 FDA-defined snapshot algorithm.

Statistical analysis of the primary efficacy endpoint was described in the Week 48 Statistical Analysis Plan and reported in the previous interim CSRs.

Analysis of all secondary efficacy endpoints was reported in the previous interim CSRs. Analysis of HIV-1 RNA-related endpoints based on the snapshot algorithm was not repeated in the final analysis. The proportion of subjects with HIV-1 RNA < 50 copies/mL was analyzed using 2 methods for imputing missing HIV-1 RNA values: Missing Failure (M F) and Missing Excluded (M E), as specified in Appendix 16.1.9, Statistical Analysis Plan.

Analysis of CD4 cell counts was based on on-treatment data (ie, up to 1 day after the last dose date of study drug) using the Full Analysis Set (FAS) for the Double-Blind Phase analysis and the All F/TAF Analysis Set for the all F/TAF analysis.

Changes from baseline in CD4 cell count at each visit were summarized by treatment group using descriptive statistics based on observed data (ie, missing was excluded). For the Double-Blind Phase, differences in changes from baseline in CD4 cell count between the 2 treatment groups and their associated 95% CIs were constructed using analysis of variance (ANOVA) models, including treatment and third agent stratum (boosted PIs vs. others) as fixed effects in the model.

Pharmacokinetics:

No PK assessments were performed for this report. All necessary PK analyses were performed as part of the Week 48 interim analysis and not repeated in this final analysis.

Safety:

The Safety Analysis Set included all randomized subjects who received ≥ 1 dose of study drug. All safety data collected on or after the date of the first dose of study drug up to the last dose date of study drug plus 30 days were included in the safety summaries. Safety data were summarized for the subjects in the Safety Analysis Set for the Double-Blind Phase analysis and the All F/TAF Analysis Set for the all F/TAF analysis. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1. All safety data was included in data listings. No treatment comparison was performed for all F/TAF analysis.

For both the Double-Blind Phase and all F/TAF analyses, percentage change 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.

Percentage changes from baseline in hip BMD and spine BMD, the 2 key secondary safety endpoints, were summarized by treatment group and visit using descriptive statistics for subjects in the Hip and Spine DXA Analysis Sets, 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.

Patient-Reported Outcomes:

Patient-reported outcome measures were evaluated in the previous analyses and were not repeated in this final analysis.

SUMMARY OF RESULTS:

Subject Disposition: A total of 663 subjects were randomized, of whom 663 and received at least 1 dose of study drug in the Double-Blind Phase (F/TAF+3rd Agent 333 subjects; in the FTC/TDF+3rd Agent group 330 subjects; Section 15.1, Table 1). A total of 571 subjects (F/TAF+3rd Agent 85.9%, 286 of 333 subjects; FTC/TDF+3rd Agent 86.4%, 285 of 330 subjects) completed study drug in the Double-Blind Phase. A total of 64 subjects (F/TAF+3rd Agent 9.9%, 33 subjects; FTC/TDF+3rd Agent 9.4%, 31 subjects) entered the OL Extension Phase, all of whom received ≥ 1 dose of OL F/TAF+3rd Agent.

A total of 92 subjects (F/TAF+3rd Agent 14.1%, 47 subjects; FTC/TDF+3rd Agent 13.6%, 45 subjects) prematurely discontinued study drug in the Double-Blind Phase. The most common reasons for premature discontinuation of study drug during the Double-Blind Phase were withdrawal of consent (F/TAF+3rd Agent 6.0%, 20 subjects; FTC/TDF+3rd Agent 5.5%, 18 subjects), investigator's discretion (F/TAF+3rd Agent 1.8%, 6 subjects; FTC/TDF+3rd Agent 2.1%, 7 subjects), AE (F/TAF+3rd Agent 2.4%, 8 subjects; FTC/TDF+3rd Agent 1.2%, 4 subjects), and protocol violation (F/TAF+3rd Agent 0.9%, 3 subjects; FTC/TDF+3rd Agent 2.7%, 9 subjects).

A total of 22 subjects (F/TAF+3rd Agent 36.4%, 12 of 33 subjects; FTC/TDF+3rd Agent→F/TAF+3rd Agent 32.3%, 10 of 31 subjects) prematurely discontinued study drug in the OL Extension Phase. The reasons for premature discontinuation of study drug during the OL Extension Phase were investigator's discretion (F/TAF+3rd Agent 24.2%, 8 subjects; FTC/TDF+3rd Agent→F/TAF+3rd Agent 29.0%, 9 subjects), withdrawal of consent (F/TAF+3rd Agent 9.1%, 3 subjects; FTC/TDF+3rd Agent→F/TAF+3rd Agent 3.2%, 1 subject), and lost to follow up (F/TAF+3rd Agent 3.0%, 1 subject).

Subject Demographics and Baseline Disease Characteristics: In the Double-Blind Phase, demographic and general baseline characteristics were similar between the 2 treatment groups with the exception of ethnicity; a statistically significantly higher percentage of subjects in the FTC/TDF+3rd Agent group were Hispanic or Latino (23.6%, 78 subjects) compared with the F/TAF+3rd Agent group (14.4%, 48 subjects; p 0.002) (Section 15.1, Table 3.1). Most subjects in the Safety Analysis Set were male (84.6%), with a median age of 49 years (range: 22 to 79 years); most were either white (75.0%) or black (20.5%), and most were not Hispanic/Latino (81.0%). The median (Q1, Q3) value for body mass index at baseline was 26.3 (23.7, 29.7) kg/m^2.

Baseline disease characteristics were generally similar between the 2 treatment groups in the Double-Blind Phase (Section 15.1, Table 4.1). Most subjects [98.8%] in the Safety Analysis Set had HIV-1 RNA < 50 copies/mL. Overall, the median (Q1, Q3) baseline CD4 cell count was 646 (491, 835) cells/µL. The most common HIV risk factor category was homosexual sex (68.5% of subjects). Few subjects (7.6%) had symptomatic HIV-1 infection, and 9.8% were diagnosed with AIDS.

At baseline, the median (Q1, Q3) $eGFR_{CG}$ was 99.8 (83.8, 120.6) mL/min. As detailed in the Week 96 Interim CSR, most subjects (91.1%) had no proteinuria (Grade 0) by dipstick on urinalysis. Values for eGFRCG and eGFRCKD EPI, creatinine were similar between the 2 treatment groups.

The demographic and baseline characteristics of the All F/TAF Analysis Set were similar to those of the Safety Analysis Set (Section 15.1, Tables 3.2 and 4.2).

Efficacy Results:

The rates of virologic success (HIV 1 RNA < 50 copies/mL) at Week 96 as assessed by M F and M E analyses were high and similar in both treatment groups (M F: F/TAF+3rd Agent 89.5%, FTC/TDF+3rd Agent 92.1%; M E: F/TAF+3rd Agent 98.0%, FTC/TDF+3rd Agent 99.3%; stratum weighted differences in response rates between treatment groups were: M F: 2.6%, 95% CI: 7.1% to 1.8%; M E: 1.3%, 95% CI: 3.3% to 0.7%) (Section 15.1, Tables 8 and 9.1).

The rates of virologic success (HIV 1 RNA < 50 copies/mL) at Week 96 as assessed by M E in the All F/TAF Analysis Set are consistent with results observed in the Double-Blind Phase of the study (Section 15.1, Table 9.2).

For the Double-Blind Phase of the study, mean changes from baseline in CD4 cell count are shown in Section 15.1, Figure 4.1 for the Safety Analysis Set and summarized in Section 15.1, Table 10.1 for the FAS. CD4 cell counts increased modestly from baseline through Week 96, and mean increases were similar between treatment groups at all time points. At Week 96, mean (SD) increases from baseline in CD4 cell count for subjects in the FAS, based on observed data, were 50 (198.7) cells/μL in the F/TAF+3rd Agent group and 46 (169.4) cells/μL in the FTC/TDF+3rd Agent group. The difference in least squares means was 3 (95% CI: 26 to 33) cells/μL.

Mean changes from baseline in CD4 cell count in the All F/TAF Analysis Set are consistent with results observed in the Double-Blind Phase of the study (Section 15.1, Table 10.2).

Resistance development through the end of study was rare in the F/TAF+3rd Agent and FTC/TDF+3rd Agent groups. In the F/TAF+3rd Agent group, 1 of 6 subjects analyzed (0.3%) developed M184V in reverse transcriptase through the end of the study with reduced susceptibility to emtricitabine. In the FTC/TDF+3rd Agent group, 0 of 3 subjects analyzed developed resistance to any components of their regimen (Appendix 16.1, Virology Listing 1).

Safety Results: Overall, F/TAF+3rd Agent was generally well tolerated by subjects as evidenced by the infrequent discontinuations due to AEs and the low number of study drug-related SAEs. Adherence to study drug was high in both study phases throughout the study, with a median study drug adherence rate during the study > 97% for all treatment groups (Tables 7.1 and 7.2).

Double-Blind Phase Analyses

Subjects in the Safety Analysis Set were exposed to F/TAF+3rd Agent or FTC/TDF+3rd Agent for a median (Q1, Q3) of 108.1 (105.1, 114.1) and 108.1 (105.0, 114.6) weeks, respectively (Section 15.1, Table 5.1), with a maximum duration of exposure around 120 weeks.

Adverse Events

Similar percentages of subjects in each group had any AE (F/TAF+3rd Agent 91.9%, 306 subjects; FTC/TDF+3rd Agent 89.1%, 294 subjects; Section 15.1, Table 11.1). The most commonly reported AEs were as follows (Section 15.1, Table req12201.1):

- F/TAF+3rd Agent group upper respiratory tract infection (16.2%, 54 subjects), diarrhea (13.5%, 45 subjects), and nasopharyngitis (12.9%, 43 subjects)
- FTC/TDF+3rd Agent group upper respiratory tract infection (20.3%, 67 subjects), diarrhea (12.7%, 42 subjects), and back pain and sinusitis (each 8.5%, 28 subjects)

The majority of AEs were Grade 1 or 2 (Section 15.1, Table 11.1). Similar percentages of subjects in each treatment group had any Grade 3 or 4 AEs (F/TAF+3rd Agent 8.1%, 27 subjects; FTC/TDF+3rd Agent 8.5%, 28 subjects) or any AE considered related to study drug (F/TAF+3rd Agent 13.2%, 44 subjects; FTC/TDF+3rd Agent 15.5%, 51 subjects). The majority of study drug-related AEs were Grade 1. The incidence of Grade 3 or 4 AEs considered related to study drug was low in both treatment groups (0.6%, 2 subjects in each).

Serious adverse events (SAEs) were reported for similar percentages of subjects in each treatment group (F/TAF+3rd Agent 8.7%, 29 subjects; FTC/TDF+3rd Agent 9.4%, 31 subjects). The incidence of SAEs considered related to study drug was low in both treatment groups (F/TAF+3rd Agent no subjects; FTC/TDF+3rd Agent 0.3%, 1 subject) (Section 15.1, Table 11.1).

Adverse events that led to discontinuation of study drug were reported for 8 subjects (2.4%) in the F/TAF+3rd Agent group and 4 subjects (1.2%) in the FTC/TDF+3rd Agent group (Section 15.1, Table 11.1). Adverse events leading to discontinuation of study drug considered related to study drug were reported for 2 subjects in the F/TAF+3rd Agent group and 4 subjects in the FTC/TDF+3rd Agent group (Appendix 16.2, Listing 20).

There were 3 treatment-emergent deaths: 2 subjects in the F/TAF+3rd Agent treatment group and 1 subject in the FTC/TDF+3rd Agent treatment group (Section 15.1, Table 11.1). One subject in the F/TAF+3rd Agent group died as a result of malignant lymphoma/high lipase. The other subject in the F/TAF+3rd Agent group died as a result of respiratory failure. One subject in the FTC/TDF+3rd Agent group died as a result of drowning. None of the deaths was considered study drug-related by the investigator (Appendix 16.2, Listing 19.1).

One confirmed pregnancy was reported (F/TAF+3rd Agent treatment group) (Appendix 16.2, Listing 33), which resulted in delivery of a healthy baby girl (a narrative is provided in Section 15.2).

Bone Safety

There were increases from baseline in mean (SD) BMD in both the hip and spine in the F/TAF+3rd Agent group through Week 120, compared with minimal changes in the FTC/TDF+3rd Agent group ($p < 0.001$). Mean (SD) percentage changes from baseline at Week 96 in BMD were as follows (Section 15.1, Tables 27.1.1 and 27.2.1):

- **Hip:** F/TAF+3rd Agent 1.856% (3.2195%); FTC/TDF+3rd Agent 0.289% (2.9912%)
- **Spine:** F/TAF+3rd Agent 2.159% (3.8374%); FTC/TDF+3rd Agent 0.109% (3.6738%)

Serum levels of PTH, a hormone involved in both bone formation and resorption, decreased slightly from baseline in the F/TAF+3rd Agent group but showed a slight increase from baseline in the FTC/TDF+3rd Agent group ($p < 0.001$ for the difference between groups from Weeks 36 through 108; Section 15.1, Table 25.23.1).

Renal Safety

In the F/TAF+3rd Agent group, no subject had a renal AE that was considered serious or resulted in discontinuation of study drug (Section 15.1, Tables 19.1 and 20.0); 2 subjects had Grade 1 or 2 proteinuria AEs considered study drug-related by the investigator (Appendix 16.2, Table 15.1). In the FTC/TDF+3rd Agent group, 1 subject had an SAE of nephrolithiasis considered study drug-related by the investigator and 1 subject had an SAE of renal colic considered not related to study drug (Section 15.1, Table 18.1; Appendix 16.2, Listing 19.1); neither of these SAEs led to study drug discontinuation. Additionally, 1 subject had a nonserious renal AE of blood creatinine increased and 1 subject had a nonserious AE of renal tubular disorder; both of these AEs were considered study drug-related by the investigator, and each led to discontinuation of study drug (Appendix 16.2, Listing 17).

No cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported in the F/TAF+3rd Agent group during the study (compared with 1 case in the FTC/TDF+3rd Agent group) (Section 15.1, Table 12.1).

For subjects who switched to F/TAF+3rd Agent, there were decreases from baseline in serum creatinine at all time points through Week 96 compared with minimal changes from baseline among subjects who remained on an FTC/TDF+3rd Agent regimen. At Week 96, mean (SD) changes from baseline in serum creatinine were as follows: F/TAF+3rd Agent 0.08 (0.239) mg/dL; FTC/TDF+3rd Agent 0.04 (0.120) mg/dL (p 0.003) (Section 15.1, Table 28.1).

There were increases from baseline in $eGFR_{CG}$ values in the F/TAF+3rd Agent group through Week 96 compared with minimal changes from baseline in the FTC/TDF+3rd Agent group. Median changes from baseline at Week 96 were as follows: F/TAF+3rd Agent 10.0 mL/min, FTC/TDF+3rd Agent 4.0 mL/min; $p < 0.001$ (Section 15.1, Table 29.1). These eGFR values remained consistent through Week 120.

As reported in the Week 96 Interim CSR, there were decreases from baseline in median UPCR values at most time points through Week 96 in the F/TAF+3rd Agent group compared with increases from baseline at most time points in the FTC/TDF+3rd Agent group ($p < 0.001$ for difference in percentage change from baseline in median values between groups at all time points).

In the F/TAF group, of subjects with a UPCR > 200 mg/g at Baseline (n 22), 83.3% (15 subjects) had a UPCR ≤ 200 mg/g at Week 96. In the FTC/TDF group, of subjects with UPCR > 200 mg/g at Baseline (n 19), 20.0% (3 subjects) had a UPCR ≤ 200 mg/g at Week 96. The difference between the 2 treatment groups was significant ($p < 0.001$). This trend continued through the last value on treatment (Section 15.1, Table 30).

Laboratory Abnormalities

There were no clinically relevant changes from baseline or differences between treatment groups in median values for hematology and clinical chemistry parameters. 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 group had at least 1 laboratory abnormality reported during the study (F/TAF+3rd Agent 96.7%, 320 subjects; FTC/TDF+3rd Agent 93.0%, 306 subjects); most reported abnormalities were Grade 1 or Grade 2. Percentages of laboratory abnormalities of any grade were balanced across treatment groups for most chemistry, hematology, and urinalysis parameters (Section 15.1, Table 21.1). Similar percentages of subjects in the F/TAF+3rd Agent group and the FTC/TDF+3rd Agent group had Grade 3 or 4 abnormalities (F/TAF+3rd Agent 33.2%; FTC/TDF+3rd Agent 29.8%) (Section 15.1, Table 22.1).

Metabolic Laboratory Parameters

There were increases from baseline in median fasting values of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides in the F/TAF+3rd Agent group at both Week 48 and Week 96, compared with little change from baseline in these parameters in the FTC/TDF+3rd Agent group. Differences between the groups were statistically significant.

Median (Q1, Q3) changes from baseline at Week 96 for the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent group were as follows: total cholesterol 14 (7, 30) mg/dL versus 1 (16, 16) mg/dL; LDL cholesterol 14 (1, 29) mg/dL versus 4 (10, 16) mg/dL; and triglycerides 11 (16, 49) mg/dL versus 2 (29, 33) mg/dL (Section 15.1, Tables 26.1.1, 26.2.1, and 26.5.1, respectively). Where data was available, similar findings were observed through Week 120. The changes were not considered clinically relevant.

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

Open-Label Phase Analyses

In the OL phase, for the F/TAF+3rd Agent group, the results described are cumulative and reported from the study start. Subjects in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group were rebaselined at the start of the OL F/TAF.

The median (Q1, Q3) duration of exposure to F/TAF was 108.2 (104.5, 115.3) weeks for the All F/TAF group, 108.4 (105.3, 115.3) weeks for the F/TAF group, and 37.4 (19.0, 84.7) weeks for the F/TDF→F/TAF group. The maximum duration of exposure was 227.4 weeks for the All F/TAF group and the F/TAF group, and 123.3 weeks for the F/TDF→F/TAF group (Section 15.1, Table 5.2).

Adverse Events

F/TAF+3rd Agent Group

Throughout the study, at least 1 AE was reported for most subjects in the F/TAF+3rd Agent group (91.9%, 306 of 333 subjects; Section 15.1, Table 11.2). The most commonly reported AEs were upper respiratory tract infection (16.5%, 55 subjects), and diarrhea and nasopharyngitis (each in 13.8%, 46 subjects) (Section 15.1, Table req12201.2).

AEs of Grade 1 or 2 severity were reported for the majority of subjects (Section 15.1, Table 11.2). At least 1 Grade 3 or 4 AE was reported in 27 subjects (8.1%). The percentage of subjects that had any AE considered study drug-related by the investigator was 13.2% (44 subjects). The majority of AEs considered study drug-related were Grade 1. The incidence of Grade 3 or 4 AEs considered related to study drug was low (2 subjects).

Serious adverse events were reported for 29 subjects, none of which were considered study drug-related by the investigator (Section 15.1, Table 11.2).

Adverse events that led to discontinuation of study drug were reported for 8 subjects. Study drug-related AEs leading to discontinuation of study drug were reported for 2 subjects during the double-blind phase (Appendix 16.2, Listing 20).

Two treatment-emergent deaths were reported in the F/TAF+3rd Agent group (Section 15.1, Table 11.2). Both occurred in the double-blind phase and are described above.

During the OL phase, there were no confirmed pregnancies reported in subjects in the F/TAF+3rd Agent group (Appendix 16.2, Listing 33).

FTC/TDF+3rd Agent→F/TAF+3rd Agent Group

At least 1 AE was reported for most subjects in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group (71.0%, 22 of 31 subjects; Section 15.1, Table 11.2). The most commonly reported AEs were onychomycosis and sinusitis (each in 3 subjects), and nasopharyngitis, back pain, cough, arthralgia, influenza, syphilis, insomnia, influenza-like illness, and fungal skin infection (each in 2 subjects) (Section 15.1, Table req12201.2).

The majority of AEs reported were Grade 1 or 2 (Section 15.1, Table 11.2). Grade 3 or 4 AEs were reported for 2 subjects. No subject had any study drug-related AE.

Serious adverse events were reported for 3 subjects, none of which were considered study-drug related (Section 15.1, Table 11.2).

No AEs leading to discontinuation of study drug were reported (Section 15.1, Table 11.2).

No treatment-emergent deaths were reported in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group (Section 15.1, Table 11.2).

During the OL phase, there were no confirmed pregnancies reported in subjects in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group (Appendix 16.2, Listing 33).

Bone Safety

F/TAF+3rd Agent Group

After Week 96, it appeared that the progressive increases in BMD noted above continued. There were further increases from baseline in mean (SD) BMD in both the hip and spine in the F/TAF+3rd Agent group through Week 120 as follows (Section 15.1, Tables 27.1.2 and 27.2.2):

- **Hip:** F/TAF+3rd Agent 1.894% (3.4535%)
- **Spine:** F/TAF+3rd Agent 2.787% (4.0311%)

FTC/TDF+3rd Agent→F/TAF+3rd Agent Group

The number of subjects included in the Week 96 analysis set were too small to allow meaningful conclusions (n 7); however, mean (SD) percentage changes from baseline at Week 96 in BMD were as follows (Section 15.1, Tables 27.1.2 and 27.2.2):

- **Hip:** FTC/TDF+3rd Agent→F/TAF+3rd Agent 2.096% (2.5241%)
- **Spine:** FTC/TDF+3rd Agent→F/TAF+3rd Agent 1.545% (4.3557%)

Renal Safety

F/TAF+3rd Agent Group

The renal safety profile of F/TAF through the OL Extension Phase was mostly unchanged from that reported in the Double-Blind Phase, with no subjects in the F/TAF+3rd Agent group having a study-drug-related, renal AE or SAE, or renal AE leading to premature study drug discontinuation (Section 15.1, Tables 12.2, 15.2, 18.2, and 20.2), and similar renal laboratory parameter findings through the end of the study (Section 15.1, Tables 28.2 and 29.2). No cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported in the F/TAF+3rd Agent group during the study (Section 15.1, Table 12.2).

There was minimal change from baseline in serum creatinine throughout the OL phase. At Week 96, mean (SD) change from baseline in serum creatinine was 0.08 (0.239) mg/dL (Section 15.1, Table 28.2).

There were increases from baseline in $eGFR_{CG}$ values through Week 96; median change from baseline at Week 96 was 10.0 mL/min (Section 15.1, Table 29.2). Similar findings were observed through the end of the study.

FTC/TDF+3rd Agent→F/TAF+3rd Agent Group

No study-drug-related, renal-related AEs, renal AEs or SAEs, or renal AEs leading to premature study drug discontinuation were reported for subjects in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group (Section 15.1, Tables 15.2, 18.2, and 20.2, respectively). No cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported in the FTC/TDF+3rd Agent→F/TAF+3rd Agent Group during the OL phase of the study (Section 15.1, Table 12.2).

There were minimal changes in serum creatinine from rebaseline after switching from FTC/TDF+3rd Agent to F/TAF+3rd Agent. At Week 96, the mean (SD) change from baseline in serum creatinine was 0.06 (0.100) mg/dL (Section 15.1, Table 28.2). There were increases from baseline in $eGFR_{CG}$ values in the F/TAF+3rd Agent group through Week 96; median changes from baseline at Week 96 were 3.0 mL/min (Section 15.1, Table 29.2). Similar findings were observed through Week 120.

Laboratory Abnormalities

The laboratory parameter safety profile of the F/TAF+3rd Agent group through the OL Extension Phase was mostly unchanged from that reported in the Double-Blind Phase, with minimal or no change in the incidence of any laboratory abnormality or Grade 3 or 4 laboratory abnormalities (Section 15.1, Tables 21.2 and 22.2).

In the FTC/TDF+3rd Agent→F/TAF+3rd Agent group, there were no clinically relevant changes from baseline median values for hematology and clinical chemistry parameters.

Most subjects in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group had at least 1 laboratory abnormality reported (79.3%, 23 subjects); most reported abnormalities were Grade 1 or Grade 2 (Section 15.1, Table 21.2). The percentage of subjects in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group with Grade 3 or 4 abnormalities was 20.7% (Section 15.1, Table 22.2).

Metabolic Laboratory Parameters

Metabolic laboratory results are summarized in Section 15.1, Tables 26.1.2, 26.2.2, 26.3.2, 26.4.2, 26.5.2, and 26.6.2. The laboratory parameter safety profile of the F/TAF+3rd Agent group through the OL Extension Phase was mostly unchanged from that reported in the Double-Blind Phase. The number of subjects in the FTC/TDF+3rd Agent→F/TAF+3rd Agent group was too small to draw metabolic laboratory conclusions.

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

CONCLUSIONS: The conclusions from this final analysis are as follows:

- In both treatment groups, as expected in virologically suppressed subjects, mean (SD) increases in CD4 cell counts from baseline were modest and similar at Week 96 in the double-blind phase of the study (F/TAF+3rd Agent 50 [198.7] cells/μL; FTC/TDF+3rd Agent 46 [169.4] cells/μL) and remained consistent throughout the OL Extension Phase in both the F/TAF+3rd Agent and FTC/TDF+3rd Agent→F/TAF+3rd Agent groups.
- Resistance development to F/TAF+3rd Agent or FTC/TDF+3rd Agent was rare. A single subject developed HIV-1 resistance in the F/TAF+3rd Agent group (M184V in RT) before Week 48. No subject developed resistance after Week 48.
- In all treatment groups study drugs were well tolerated, with low rates of SAEs and AEs leading to study drug discontinuation.
- Renal laboratory parameters improved upon switching from FTC/TDF to F/TAF.
- Spine and hip BMD improved upon switching from FTC/TDF to F/TAF.
- Greater increases from baseline in fasting total cholesterol, fasting LDL cholesterol, and fasting triglycerides were observed in the F/TAF group.