FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Randomized, Double-Blind Switch Study to Evaluate the Safety and Efficacy of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) Fixed Dose Combination (FDC) in HIV-1 Positive Subjects who are Virologically Suppressed on Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF)
Name of Test Drug:	Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF; Odefsey® [ODE])
Dose and Formulation:	Fixed-dose combination tablet of FTC/RPV/TAF (200/25/25 mg)
Indication:	HIV-1 infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-366-1216
Phase of Development:	Phase 3b
IND No.: **EudraCT No.:**	123098 2014-004545-27
ClinicalTrials.gov Identifier:	NCT02345252
Study Start Date:	26 January 2015 (First Subject Screened)
Study End Date:	22 June 2016 (Last Subject Last Observation for the Primary Endpoint) 09 January 2019 (Last Subject Last Observation for this Report)

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Report Date:	30 July 2019	
Previous Report Date(s):	12 October 2017 (Interim Week 96 Clinical Study Report) 15 August 2016 (Interim Week 48 Clinical Study Report)	

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS
Study GS-US-366-1216
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b, Randomized, Double-Blind Switch Study to Evaluate the Safety and Efficacy of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) Fixed Dose Combination (FDC) in HIV-1 Positive Subjects who are Virologically Suppressed on Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF)

Investigators: This is a multicenter study.

Study Centers: Subjects were enrolled at 119 sites in 11 countries: 79 sites in the United States (US), 10 in Germany, 7 in Canada, 7 in Spain, 6 in the United Kingdom, 3 in Belgium, 2 in Italy, 2 in Switzerland, 1 in France, 1 in the Netherlands, and 1 in Sweden.

Publications:

Hagins D, Orkin C, Daar ES, Mills A, Brinson C, DeJesus E, et al. Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC, and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC, and TDF: 96-week results from two randomized clinical trials. HIV Medicine 2018;19(10):724-733.

Mills A, Brinson C, Martorell C, Crofoot G, Daar E, Osiyemi O, et al. Switching to RPV/FTC/TAF from RPV/FTC/TDF or EFV/FTC/TDF: Week 96 Results. Conference on Retroviruses and Opportunistic Infections, Boston. March 4-7, 2018, Abstract 504.

Arribas JR, Rockstroh J, Post, Yazdanpanah Y, Cavassini, DeJesus E, et al. Bone and renal safety of switching to rilpivirine/emtricitabine/tenofovir alafenamide (RPV/FTC/TAF) from single-tablet regimens (STRs) containing efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) or rilpivirine/emtricitabine/tenofovir disoproxil fumarate (RPV/FTC/TDF): Week 48 subgroup analysis in patients at risk of or with comorbidities. Abstract accepted for presentation at the 16th European AIDS Conference, 2017 25-27 October Milan, Italy.

Porter DP, Kulkarni R, Cao H, SenGupta D, White KL. No Emergent Resistance in HIV-1 Virologically-Suppressed Subjects Who Switched to RPV/FTC/TAF [Poster 1381]. ID Week™ (Infectious Diseases Society of America) 2017 4–8 October; San Diego, CA.

Wohl D, Kulkarni R, Garner W, White KL, Porter DL. Viral Blips Were Infrequent in HIV 1-Infected Virologically-Suppressed Adults Treated with Tenofovir Alafenamide or Tenofovir DF Rilpivirine-Containing Regimens [Poster 1384]. ID Week™ (Infectious Diseases Society of America) 2017 4–8 October; San Diego, CA.

DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, Molina J-M, et al. Efficacy and Safety of Switching to RPV/FTC/TAF in Older Adults. 8th International Workshop on HIV and Aging 2017 2-3 October, New York, New York.

Molina JM, DeJesus E, Rijnders B, Post FAV, B., Stoeckle M, Thalme A, et al. Efficacy and

Safety of Switching From RPV/FTC/TDF or EFV/FTC/TDF to RPV/FTC/TAF in Black Adults [Presentation MOPEB0291]. 9th IAS Conference on HIV Science 2017 23–26 July Paris, France.

Rockstroh J, Orkin C, Yazdanpanah Y, Di Perri GDS, P. E., Arribas JR, Brinkman K, et al. Switching From TDF to TAF Improves Bone and Renal Safety Independent of Age, Sex, Race, or 3rd Agent: Results From Pooled Analysis (N=3816) of Virologically Suppressed HIV-1 Infected Adults [Presentation MOPEB0289]. 9th IAS Conference on HIV Science; 2017 23-26 July Paris, France.

Orkin C, DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. Published Online 01 March. Available at: http://dx.doi.org/10.1016/S2352-3018(17)30031-0 The Lancet HIV 2017:1-10.

Majeed SR, Shao Y, Garner W, Scott J, Pérez-Ruixo C, SenGupta D, et al. Evaluation of RPV/FTC/TAF Exposure-Efficacy and Exposure-Safety Relationships [Poster 427]. Conference on Retroviruses and Opportunistic Infections (CROI) 2017 13-16 February; Seattle, WA.

Hagins D, Mills A, Martorell C, Walmsley S, Gallant J, Tebas P, et al. Efficacy and Safety of Switching to RPV/FTC/TAF in Women [Abstract 12]. 7th International Workshop on HIV & Women; 2017 11-12 February; Seattle, Washington.

Orkin C, DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, et al. 48 Week Results from two studies: Switching to RPV/FTC/TAF from EFV/FTC/TDF (Study 1160) or RPV/FTC/TDF (Study 1216) [Presentation]. HIV Glasgow; 2016 23-26 October; Glasgow, United Kingdom.

Study Period:

26 January 2015 (First Subject Screened)
22 June 2016 (Last Subject Last Observation for the Primary Endpoint)

09 January 2019 (Last Subject Last Observation for this Report)

Phase of Development: Phase 3b

Objectives:

Study GS-US-366-1216 was conducted to evaluate the efficacy, safety, and tolerability of switching to emtricitabine (FTC)/rilpivirine (RPV)/tenofovir alafenamide (TAF) (FTC/RPV/TAF fixed-dose combination [FDC] tablet; Odefsey® [ODE]) from FTC/RPV/tenofovir disoproxil fumarate (TDF) FDC tablet (FTC/RPV/TDF FDC; Complera® [CPA]/Eviplera®) in virologically suppressed, HIV-infected subjects.

The primary objective of this study was as follows:

- To evaluate the noninferiority of switching to ODE as compared to continuing CPA in virologically suppressed HIV-1 infected subjects as determined by maintaining HIV-1 RNA < 50 copies/mL at Week 48 (using the US Food and Drug Administration-defined snapshot algorithm)

The secondary objectives of this study were as follows:

- To determine the safety of the 2 treatment groups as determined by the percent change from baseline in hip and spine bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) at Weeks 48 and 96 in a subset of subjects
- To evaluate the safety and tolerability of the 2 treatment groups through Week 48
- To evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Week 96

This final report describes results obtained until after the last subject completed or discontinued from the study.

Methodology: This was a randomized, double-blind, multicenter study to evaluate the efficacy, safety, and tolerability of ODE versus continuing CPA in HIV-infected subjects who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of CPA for ≥ 6 consecutive months at screening.

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

- **Treatment Group 1**: ODE (FTC/RPV/TAF 200/25/25 mg) FDC tablet once daily + placebo-to-match CPA once daily
- **Treatment Group 2**: CPA (FTC/RPV/TDF 200/25/300 mg) FDC tablet once daily + placebo-to-match ODE once daily

Subjects were treated for at least 96 weeks. After the last subject completed the Week 96 visit and Gilead Sciences (Gilead) provided unblinded treatment assignments to the investigators, all subjects attended the clinic for an unblinding visit. At this visit, subjects were given the option to receive open-label ODE for up to an additional 48 weeks. In countries where ODE was not commercially available, subjects were given the option to receive open-label ODE and attend visits every 12 weeks until ODE became commercially available, or until Gilead elected to discontinue the study, whichever occurred first. Subjects who completed the study through the unblinding visit and did not wish to receive open-label ODE were required to return to the clinic 30 days after the completion of the study drug for a 30-day follow-up visit.

Number of Subjects (Planned and Analyzed):
Planned: Approximately 550 subjects (275 in each treatment group)
Analyzed: (by analysis set) (Tables 15.8.5.1 and 15.8.5.2):

Subjects, n (%)	ODE	CPA	Total
All Randomized Analysis Set	316	316	632
Safety Analysis Set	316 (100.0%)	314 (99.4%)	630 (99.7%)
Full Analysis Set (FAS)	316 (100.0%)	313 (99.1%)	629 (99.5%)
Hip DXA Substudy Analysis Set	184 (58.2%)	173 (54.7%)	357 (56.5%)
Spine DXA Substudy Analysis Set	187 (59.2%)	176 (55.7%)	363 (57.4%)
All FTC/RPV/TAF Analysis Set	316	17[a]	333
All FTC/RPV/TAF Hip DXA Analysis Set	184 (58.2%)	6 (35.3%)[a]	190 (57.1%)
All FTC/RPV/TAF Spine DXA Analysis Set	187 (59.2%)	6 (35.3%)[a]	193 (58.0%)

For the double-blind phase analysis, the denominator for percentages was based on the number of subjects in the All Randomized Analysis Set. One subject was randomized and treated but excluded from the FAS.
For the All FTC/RPV/TAF Analysis, the denominator for percentages was based on the number of subjects in the All FTC/RPV/TAF Analysis Set.
[a] These subjects switched from CPA to ODE.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were HIV-infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of CPA for ≥ 6 consecutive months prior to screening, with no documented resistance to any of the study agents, and who had an estimated glomerular filtration rate calculated according to the Cockcroft-Gault formula ($eGFR_{CG}$) ≥ 50 mL/min.

Duration of Treatment: Subjects were treated for at least 96 weeks. After the last subject completed the Week 96 visit, all subjects attended an unblinding visit, at which point subjects were given the option to receive open-label ODE for up to an additional 48 weeks. In countries where ODE was not commercially available, subjects were given the option to receive open-label ODE and attend visits every 12 weeks until ODE became commercially available, or until Gilead elected to discontinue the study, whichever occurred first.

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

ODE (FTC/RPV/TAF 200/25/25 mg FDC tablet) + placebo-to-match CPA administered orally once daily with food at approximately the same time each day

ODE Batch Numbers (double-blind phase): EF1401B2, EF1505B1, EF1506B1R, EF1513B1

Placebo-to-Match CPA Batch Numbers: BY1402B1, BY1601B1

ODE Batch Number (open-label extension phase): EF1701B1

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

CPA (FTC/RPV/TDF 200/25/300 mg FDC tablet) + placebo-to-match ODE administered orally once daily with food at approximately the same time each day

CPA Batch Numbers: BY1401B1, BY1501B1, TDWW, BY1602B1, BY1701B1

Placebo-to-Match ODE Batch Numbers: EF1406B1, EF1504B1, EF1514B1, EF1516B1, EF1601B1

Criteria for Evaluation:

Efficacy: The primary and secondary efficacy endpoints were presented in the GS-US-366-1216 Interim Weeks 48 and 96 Clinical Study Reports (CSRs).

Efficacy endpoints evaluated for this final analysis were as follows:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at each visit as defined by 2 different methods for imputing missing HIV-1 RNA values:
  - Missing = Failure (M = F); in this approach, all missing data was treated as virologic failure (ie, HIV-1 RNA ≥ 50 copies/mL)
  - Missing = Excluded (M = E); in this approach, all missing data was excluded in the computation of virologic response (ie, missing data points were excluded from both the numerator and denominator in response rate computation)
- The change from baseline in CD4% at each visit

Pharmacokinetics: No pharmacokinetic (PK) assessments were performed for this report.

Safety:

The safety endpoints evaluated for this final analysis are presented in this section.

Safety assessments included adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, DXA scans (hip and spine BMD), renal safety tests (serum creatinine and $eGFR_{CG}$), and concomitant medications.

Statistical Methods:

Efficacy:

The Full Analysis Set (FAS) was the primary efficacy analysis set and included all subjects who were randomized into the study, received at least 1 dose of study drug, and were on FTC/RPV/TDF prior to the Screening visit.

The All FTC/RPV/TAF Analysis Set was the primary efficacy analysis set for All FTC/RPV/TAF efficacy analyses and included all subjects who are randomized and received at least 1 dose of double-blinded FTC/RPV/TAF during the double-blind phase or open-label FTC/RPV/TAF during the open-label extension phase.

The change from baseline in CD4 cell count was summarized by treatment group and visit using descriptive statistics for the FAS and the All FTC/RPV/TAF Analysis Set. The differences in changes from baseline in CD4 cell count between the 2 treatment groups and the associated 95% confidence intervals (CIs) were constructed using an analysis of variance model using the FAS for the double-blind phase analysis.

Virology Resistance: There were no statistical methods for virology resistance.

Pharmacokinetics: No PK analyses were performed for this report.

Safety: 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 for subjects who permanently discontinued study drug, or all available data for subjects who were still on study drug, were summarized for subjects in the Safety Analysis Set.

Safety data were summarized by treatment for the subjects in the Safety Analysis Set for the double-blind phase analysis and the All FTC/RPV/TAF Analysis Set for the All FTC/RPV/TAF analysis, unless specified otherwise.

Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 21.1. Safety data were summarized by treatment group using descriptive statistics.

SUMMARY OF RESULTS:

Subject Disposition and Demographics:

A total of 690 subjects were screened, and 632 subjects were randomized. Of these, 630 subjects received at least 1 dose of study drug and were included in the Safety Analysis Set (ODE 316 subjects; CPA 314 subjects). One subject who was randomized and received study drug (CPA group) was excluded from the FAS because of having received Atripla instead of CPA prior to the screening visit. Of the 630 subjects treated with study drug, 36 subjects received at least 1 dose of open-label ODE (ODE 19 subjects; subjects who switched from CPA to ODE: 17 subjects) during the open-label extension phase (Tables 15.8.1.1 and 15.8.5.1).

Double-Blind Phase

Of the 630 subjects treated with study drug, 14.9% (94 subjects) discontinued study drug treatment in the double-blind phase (ODE 13.3%, 42 subjects; CPA 16.6%, 52 subjects), and 13.8% (87 subjects) prematurely discontinued from the study in the double-blind phase (ODE 12.7%, 40 subjects; CPA 15.0%, 47 subjects). The most common reasons subjects prematurely

discontinued study drug were withdrawal of consent (ODE 5.7%, 18 subjects; CPA 7.0%, 22 subjects), lost to follow-up (ODE 2.2%, 7 subjects; CPA 3.2%, 10 subjects), investigator's discretion (ODE 1.9%, 6 subjects; CPA 2.2%, 7 subjects), and AE (ODE 1.6%, 5 subjects; CPA 1.9%, 6 subjects); other reasons were each recorded for less than 1% of subjects overall (Table 15.8.1.1).

The discontinuation profile was similar in both treatment groups. Through the double-blind phase, 536 subjects (85.1% of 630 treated subjects) completed study drug treatment (ODE 86.7%, 274 subjects; CPA 83.4%, 262 subjects), and 543 subjects (86.2%) completed the double-blind phase (ODE 87.3%, 276 subjects; CPA 85.0%, 267 subjects) (Table 15.8.1.1).

Demographic and general baseline characteristics were similar between the 2 treatment groups. The median age of subjects in the Safety Analysis Set was 45 years (range: 23-72 years). Most subjects were male (89.5%), white (74.9%) or black (19.0%), and not Hispanic or Latino (85.1%). The median (first quartile [Q1], third quartile [Q3]) body mass index at baseline was 25.5 (23.1, 28.4) kg/m^2 (Table 15.8.3.1).

Baseline disease characteristics were similar between the 2 treatment groups. The study enrolled a virologically suppressed, HIV-infected population; therefore, 98.3% of subjects in the Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL. The median (Q1, Q3) baseline CD4 count was 670 (521, 856) cells/μL, with approximately three-quarters (78.7%) of subjects having a baseline CD4 count ≥ 500 cells/μL; the median (Q1, Q3) baseline CD4% was 36.8% (31.2%, 41.9%). The most common HIV risk factor category was homosexual sex (79.5%); 18.3% of subjects reported heterosexual sex as the mode of infection. Most subjects (90.5%) had no proteinuria (Grade 0 by dipstick) on urinalysis. Mean (and median) values for $eGFR_{CG}$ were similar between the 2 treatment groups (mean [standard deviation; SD] $eGFR_{CG}$ at baseline: ODE 106.1 [26.18] mL/min; CPA 106.2 [29.88] mL/min) (Table 15.8.3.3).

Open-Label Extension Phase

Of the 630 subjects treated with study drug, 5.7% (36 subjects) entered the open-label extension phase and were treated (ODE 6.0%, 19/316 subjects; subjects who switched from CPA to ODE: 5.4%, 17/314 subjects) (Table 15.8.1.1).

Through the open-label extension phase, 35 subjects (97.2% of 36 subjects) completed study drug treatment (ODE 100%, 19/19 subjects; subjects who switched from CPA to ODE: 94.1%, 16/17 subjects), and all 36 subjects completed the open-label extension phase (Table 15.8.1.1).

The overall demographic and general baseline characteristics of the All FTC/RPV/TAF Analysis Set were similar to those observed for the Safety Analysis Set (Table 15.8.3.2).

The overall baseline disease characteristics of the All FTC/RPV/TAF Analysis Set were similar to those observed for the Safety Analysis Set (Table 15.8.3.4).

Efficacy Results:

Efficacy analyses with respect to the primary and secondary efficacy endpoints were presented in the GS-US-366-1216 Interim Weeks 48 and 96 CSRs. In this section, efficacy analyses, based on the FAS and the All FTC/RPV/TAF Analysis Set, for the final analyses are provided.

Double-Blind Phase

The percentage of subjects who maintained HIV-1 RNA < 50 copies/mL was high in both groups through 96 weeks, as assessed using the M = F and M = E analyses for the subjects in the FAS. For the M = F analysis, the percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 96 were as follows: ODE 90.8%; CPA 90.4% (Table 15.9.3.1.1). For the M = E analysis, the percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 96 were as follows: ODE 99.7%; CPA 99.6%. For the M = E analysis, efficacy was maintained after Week 96, as the percentage of subjects with HIV-1 RNA < 50 copies/mL were as follows: ODE ranged from 90.9% to 99.3%; CPA ranged from 75.0% to 99.3% from Weeks 108 to 144 (Table 15.9.3.1.2).

The differences in response rate between treatment groups at Week 96 were as follows: M = F: 0.4%, 95% CI: −4.3% to 5.1%; M = E: 0.0%, 95% CI: −1.6% to 1.7% (Table 15.9.3.1.1 and Table 15.9.3.1.2). For the M = E analysis, the differences in response rate between treatment groups ranged from 0.0%, 95% CI: −2.0% to 2.0% at Week 108 to 15.9%, 95% CI: −22.0% to 56.5% at Week 144 (Table 15.9.3.1.2).

Mean (SD) baseline CD4 cell counts and CD4% were similar between treatment groups (ODE 711 [278.9] cells/µL and 37.1 [8.83]%, respectively; CPA 703 [257.6] cells/µL and 35.6 [8.62]%, respectively). CD4 cell counts and CD4% were maintained in both groups; mean (SD) changes from baseline at Week 96 (FAS, observed data) were as follows: ODE 12 (180.6) cells/µL and 0.9 (4.29)%, respectively; CPA 16 (171.9) cells/µL and 1.2 (4.31)%, respectively (difference in least-squares mean: −4 cells/µL, 95% CI: −34 to 25 cells/µL and −0.3%, 95% CI −1.0 to 0.4%, respectively). Efficacy was maintained after Week 96, as the mean (SD) CD4 cell counts and CD4% changes from baseline were as follows: ODE ranged from 12 (179.2) cells/µL to 70 (162.3) cells/µL (0.4 [4.32]% to 1.0 [4.13]%); CPA ranged from 41 (205.3) cells/µL to 44 (192.0) cells/µL (1.0 [4.01]% to 1.6 [4.22]%) from Week 108 to 132 (Table 15.9.2.1 and Table 15.9.3.1). The interpretation of results obtained after Week 132 was limited since only 3 subjects in each treatment group had available data through Week 144.

Subjects who Switched to ODE in the Open-Label Extension Phase

The overall percentage of subjects who maintained HIV-1 RNA < 50 copies/mL was high through 60 weeks, as assessed using the M = E analyses for the subjects in the All FTC/RPV/TAF Analysis Set. The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 60 was 100% (Table 15.9.3.1.3). The interpretation of results obtained after Week 60 was limited since only 1 subject had available data through Week 72.

Mean (SD) baseline CD4 cell counts and CD4% in subjects who switched from CPA to ODE were: 783 (224.7) cells/µL and 38.0 (11.23)%, respectively. CD4 cell counts and CD4% were maintained in subjects who switched from CPA to ODE; mean (SD) changes from baseline at Week 60 (All FTC/RPV/TAF Analysis Set, observed data) were as follows: 75 (412.0) cells/µL and −0.8 (4.14)%, respectively (Table 15.9.2.2 and Table 15.9.3.2).

Virology Resistance Data:

Double-Blind Phase

Subjects receiving ODE: Of the 316 treated subjects from the ODE arm, 7 subjects were included in the resistance analysis population through the end of study (2.2%; 7 of 316 subjects). Of these 7 subjects, 6 had post-baseline genotypic and phenotypic data for PR/RT available. No

subjects on the ODE arm had emergent resistance to study drug.

Subjects receiving CPA: Of the 313 treated subjects from the CPA arm, 5 subjects were included in the resistance analysis population through the end of study (1.6%; 5 of 313 subjects). Of these 5 subjects, 5 had post-baseline genotypic and phenotypic data for PR/RT available. One subject developed K65R, K219K/E, and Y181C substitutions at Week 84 while on CPA treatment. No subjects on the CPA arm developed treatment-emergent drug resistance after Week 96.

Open-Label Extension Phase

None of the 17 subjects who switched from CPA to ODE in the open-label ODE phase were included in the resistance analysis population or had emergent resistance to study drug.

Pharmacokinetics Results: No PK analyses were performed for this report. All intensive PK analyses and summary statistics were included in the GS-US-366-1216 Interim Week 48 CSR.

Safety Results:

Double-Blind Phase

In subjects in the FAS who switched from CPA to ODE, ODE was generally well tolerated through a median of 118.6 weeks of exposure (Table 15.11.1.1), as evidenced by the infrequent discontinuations due to AEs (Table 15.8.1.1) and the absence of study drug-related serious adverse events (SAEs) (Table 15.11.4.3). In subjects in the FAS who continued on CPA, study drug was generally well tolerated through a median of 118.0 weeks of exposure (Table 15.11.1.1).

Adverse Events

Overall, the rates and types of AEs reported in this study were similar in the 2 groups in the Safety Analysis Set.

Adverse events were reported in similar percentages of subjects in each group (ODE 93.4%, 295 of 316 subjects; CPA 91.4%, 287 of 314 subjects). Three treatment-emergent deaths occurred during the double-blind phase: 1 subject in the ODE group died as a result of acute methamphetamine intoxication, 1 subject in the CPA group died as a result of carbon monoxide poisoning, and 1 subject in the CPA group died as a result of suicide (Table 15.11.2.1.1 and Listing 16.2.7.7). The events were not considered related to study drug. In these 3 subjects, the treatment-emergent deaths occurred prior to the Week 96 data cut and have been discussed in the previous CSRs. One treatment-emergent death occurred during the open-label extension phase (this subject had been randomized to the ODE group during the double-blind phase). This subject died as a result of adenocarcinoma (Table 15.11.2.1.2 and Listings 16.2.7.1.1 and 16.2.7.7). The event was not considered related to study drug (Listing 16.2.7.1.1).

The incidence of SAEs was low in the double-blind phase (ODE 11.4%, 36 of 316 subjects; CPA 9.2%, 29 of 314 subjects); no SAE was considered related to study drug (Table 15.11.4.1 and Table 15.11.4.3). A lower percentage of subjects in the ODE group compared with the CPA group had any AE considered related to study drug (ODE 8.9%, 28 subjects; CPA 14.6%, 46 subjects); the difference was not attributed to a specific AE or group of AEs (Table 15.11.2.3.1.1). The incidence of Grade 3 or Grade 4 AEs was low (ODE 10.4%; 33 subjects; CPA 11.8%, 37 subjects) (Table 15.11.2.2.3).

Adverse events that led to study drug discontinuation were uncommon in both groups in the double-blind phase (ODE 1.6%, 5 subjects; CPA 1.9%, 6 subjects). No AE that led to study drug discontinuation was reported for more than 1 subject in either group (Table 15.11.5.1). One subject in the CPA group had a study drug-related AE leading to study drug discontinuation (drug hypersensitivity) (Listings 16.2.7.5). This event occurred prior to the Week 96 data cut and has been discussed in the previous CSRs.

Common AEs were consistent with those expected in the study population, the known safety profiles of the study drugs, and previous clinical study experience. The most commonly reported AEs by treatment group in the double-blind phase were as follows:

- ODE: nasopharyngitis (15.5%, 49 of 316 subjects); upper respiratory tract infection (14.9%, 47 subjects); and diarrhea (10.8%, 34 subjects) (Table 15.11.2.1.3 and 15.11.2.1.5)
- CPA: nasopharyngitis (14.6%, 46 of 314 subjects); upper respiratory tract infection (14.6%, 46 of 314 subjects); and diarrhea (12.7%, 40 subjects) (Table 15.11.2.1.3 and 15.11.2.1.5)

Bone Safety

There were increases from baseline in mean (SD) BMD at the hip and spine in subjects who switched to ODE, compared with small decreases in both for subjects who remained on CPA ($p < 0.001$ for the difference between groups for both hip and spine) (Table 15.11.2.4.2.1 and Table 15.11.2.4.2.2).

Mean (SD) percentage changes at Week 120 in hip and spine BMD were as follows:

- Hip: ODE 1.674% (2.4836%); CPA −0.966% (3.0711%) (Table 15.11.2.4.2.1)
- Spine: ODE 2.228% (4.1614%); CPA −0.037% (4.1044%) (Table 15.11.2.4.2.2)

Renal Safety

Six renal SAEs were reported in the double-blind phase; these were events of acute kidney injury in 1 subject in the ODE group and 1 subject in the CPA group, an event of renal neoplasm in 1 subject in the CPA group, and events of calculus urethral, nephrolithiasis, and renal colic in 1 subject each in the ODE group (Table 15.11.4.1). All were considered unrelated to study drug (Table 15.11.4.3). No subject discontinued study drug due to a renal AE (Table 15.11.5.1). There were no cases of proximal renal tubulopathy (including Fanconi syndrome) (Table 15.11.2.1.3).

For serum creatinine, median baseline values were similar in the 2 treatment groups. At Week 132, median (Q1, Q3) changes from baseline in serum creatinine were ODE −0.01 (−0.08, 0.07) mg/dL; CPA −0.01 (−0.11, 0.08) mg/dL. The differences between groups in change from baseline in serum creatinine were not statistically significant at any time point except for Week 12 and Week 96 ($p = 0.014$ at both time points) (Table 15.11.2.4.4.1).

For $eGFR_{CG}$, median baseline values were similar in the 2 treatment groups. At Week 132, median (Q1, Q3) changes from baseline in $eGFR_{CG}$ were ODE 3.0 (−9.4, 13.7) mL/min; CPA −1.4 (−8.2, 10.3) mL/min. The differences between groups in change from baseline in $eGFR_{CG}$ were statistically significant at all time points from Week 8 through Week 120 ($p < 0.001$ at Week 120) (Table 15.11.2.4.5.1).

Laboratory Abnormalities

There were no clinically relevant changes from baseline within each treatment group, or differences between the treatment groups in median values for hematology (Tables 15.11.6.1.1.1, 15.11.6.1.2.1, 15.11.6.1.3.1, 15.11.6.1.4.1, 15.11.6.1.5.1, 15.11.6.1.6.1, 15.11.6.1.7.1, 15.11.6.1.8.1, 15.11.6.1.9.1, 15.11.6.1.10.1, 15.11.6.1.11.1, 15.11.6.1.12.1, and 15.11.6.1.13.1) or clinical chemistry parameters (Tables 15.11.6.2.1.1, 15.11.6.2.2.1, 15.11.6.2.3.1, 15.11.6.2.4.1, 15.11.6.2.5.1, 15.11.6.2.6.1, 15.11.6.2.7.1, 15.11.6.2.8.1, 15.11.6.2.9.1, 15.11.6.2.10.1, 15.11.6.2.11.1, 15.11.6.2.12.1, 15.11.6.2.13.1, 15.11.6.2.14.1, 15.11.6.2.15.1, 15.11.6.2.16.1, 15.11.6.2.17.1, and 15.11.6.2.18.1). All median values were within normal ranges through Week 132.

Most subjects had at least 1 laboratory abnormality (ODE 93.3%, 294 of 315 subjects; CPA 92.3%, 289 of 313 subjects). Most reported abnormalities were Grade 1 or Grade 2 (Table 15.11.6.4.1). A higher percentage of subjects in the ODE group than the CPA group had Grade 3 or Grade 4 abnormalities (ODE 20.6%, CPA 13.4%); the difference was predominantly due to the higher incidence of fasting low-density lipoprotein (LDL) and total cholesterol abnormalities in the ODE group. The incidence of laboratory abnormalities of any grade was balanced in both treatment groups for most chemistry and hematology parameters (Table 15.11.6.4.3).

Metabolic Laboratory Parameters

There were increases from baseline in fasting values of total cholesterol, direct LDL cholesterol, and triglycerides in the ODE group, while these parameters had little change or slight decrease in the CPA group at Week 120 (Tables 15.11.6.3.1.1, 15.11.6.3.2.1, and 15.11.6.3.5.1). There were no clinically relevant changes from baseline in median fasting values for high-density lipoprotein (HDL) cholesterol, fasting total cholesterol to HDL cholesterol ratio, or glucose in either treatment group (Tables 15.11.6.3.3.1, 15.11.6.3.4.1, and 15.11.6.3.6.1).

Median (Q1, Q3) absolute changes from baseline in fasting lipid parameters at Week 120 were as follows:

- Total cholesterol: ODE 19 (0, 34) mg/dL; CPA 3 (−11, 16) mg/dL ($p < 0.001$) (Table 15.11.6.3.1.1)
- Direct LDL cholesterol: ODE 13 (−1, 26) mg/dL, CPA 3 (−7, 15) mg/dL ($p < 0.001$) (Table 15.11.6.3.2.1)
- Triglycerides: ODE 12 (−12, 42) mg/dL, CPA 3 (−26, 31) mg/dL ($p = 0.013$) (Table 15.11.6.3.5.1)

ECG Abnormalities

Clinically significant ECG findings were reported for 8 subjects in the ODE group and 3 subjects in the CPA group (Listing 16.2.8.6). Adverse events related to ECGs were reported in 2 subjects in the ODE group and 1 subject in the CPA group (Table 15.11.2.1.3); the ECG-related AEs were nonserious (Table 15.11.4.1), were considered not related to study drug (Table 15.11.2.3.1.1), and did not result in study drug discontinuation (Table 15.11.5.1).

Body Weight

Increases in body weight were greater in the ODE group than the CPA group (Table 15.11.7.2.1).

There were no clinically relevant findings in vital signs (Tables 15.11.7.1.1, 15.11.7.1.3, 15.11.7.1.5, 15.11.7.1.7, and 15.11.7.1.9).

Subjects who Switched to ODE in the Open-Label Extension Phase

In subjects in the All FTC/RPV/TAF Analysis Set who switched from CPA to ODE, study drug was generally well tolerated through a median of 48.0 weeks of exposure (Table 15.11.1.2).

Adverse Events

No treatment-emergent deaths, SAEs, or AEs leading to study drug discontunuation occurred in subjects who switched from CPA to ODE in the open-label extension phase (Table 15.11.2.1.2, Table 15.11.4.2, and Table 15.11.5.2).

Common AEs were consistent with those expected in the study population, the known safety profiles of the study drugs, and previous clinical study experience. The most commonly reported AEs by treatment group in the open-label extension phase were as follows:

- Subjects who switched from CPA to ODE: cough (17.6%, 3 of 17 subjects); nasopharyngitis (17.6%, 3 of 17 subjects); and pyrexia (17.6%, 3 of 17 subjects) (Tables 15.11.2.1.4 and 15.11.2.1.6)

Bone Safety

Few subjects in the hip or spine DXA substudy analysis sets entered the open-label extension phase; therefore, BMD data were not summarized for the All FTC/RPV/TAF analysis.

Renal Safety

No renal SAEs were reported in subjects who switched to ODE in the open-label extension phase (Table 15.11.4.2). None of the subjects discontinued study drug due to a renal AE (Table 15.11.5.2). There were no cases of proximal renal tubulopathy (including Fanconi syndrome) (Table 15.11.2.1.4).

At Week 60, overall median (Q1, Q3) changes from baseline in serum creatinine were 0.00 (−0.05, 0.12) mg/dL (Table 15.11.2.4.4.2).

At Week 60 overall median (Q1, Q3) changes from baseline in $eGFR_{CG}$ were 0.0 (−28.2, 2.4) mL/min (Table 15.11.2.4.5.2).

Laboratory Abnormalities

There were no clinically relevant changes from baseline in median values for hematology (Tables 15.11.6.1.1.2, 15.11.6.1.2.2, 15.11.6.1.3.2, 15.11.6.1.4.2, 15.11.6.1.5.2, 15.11.6.1.6.2, 15.11.6.1.7.2, 15.11.6.1.8.2, 15.11.6.1.9.2, 15.11.6.1.10.2, 15.11.6.1.11.2, 15.11.6.1.12.2, and 15.11.6.1.13.2) or clinical chemistry parameters (Tables 15.11.6.2.1.2, 15.11.6.2.2.2, 15.11.6.2.3.2, 15.11.6.2.4.2, 15.11.6.2.5.2, 15.11.6.2.6.2, 15.11.6.2.7.2, 15.11.6.2.8.2, 15.11.6.2.9.2, 15.11.6.2.10.2, 15.11.6.2.11.2, 15.11.6.2.12.2, 15.11.6.2.13.2, 15.11.6.2.14.2, 15.11.6.2.15.2, 15.11.6.2.16.2, 15.11.6.2.17.2, and 15.11.6.2.18.2). All overall median values were within normal ranges through Week 60.

Over half of the subjects who switched from CPA to ODE had at least 1 laboratory abnormality: 58.8%, 10 of 17 subjects. Most reported abnormalities were Grade 1 or Grade 2 (Table 15.11.6.4.2). In total, 17.6%, 3 of 17 subjects had Grade 3 or Grade 4 abnormalities (Table 15.11.6.4.4).

Metabolic Laboratory Parameters

Overall, there were increases from baseline in fasting values of total cholesterol, direct LDL cholesterol, and triglycerides in total at Week 48 (Tables 15.11.6.3.1.2, 15.11.6.3.2.2, and 15.11.6.3.5.2). There were no clinically relevant changes from baseline in median fasting values for HDL cholesterol, fasting total cholesterol to HDL cholesterol ratio, or glucose (Tables 15.11.6.3.3.2, 15.11.6.3.4.2, and 15.11.6.3.6.2).

Median (Q1, Q3) absolute changes from baseline in fasting lipid parameters at Week 48 were as follows:

- Total cholesterol: 22(−8, 31) mg/dL (Table 15.11.6.3.1.2)
- Direct LDL cholesterol: 21 (8, 44) mg/dL (Table 15.11.6.3.2.2)
- Triglycerides: 8 (−42, 30) mg/dL (Table 15.11.6.3.5.2)

ECG Abnormalities

No AEs related to ECGs were reported in the subjects who switched from CPA to ODE (Table 15.11.2.1.4).

Body Weight

There were no clinically relevant findings in body weight and vital signs (Tables 15.11.7.2.2, 15.11.7.1.2, 15.11.7.1.4, 15.11.7.1.6, 15.11.7.1.8, and 15.11.7.1.10).

- CONCLUSIONS: Follow-up of subjects through the end of study (EOS) confirms the conclusions from the Week 96 analysis and are as follows:
- The percentage of subjects who maintained HIV-1 RNA < 50 copies/mL was high in both groups through 96 weeks and beyond. For the M = E analysis, efficacy was maintained after Week 96, as the percentage of subjects with HIV-1 RNA < 50 copies/mL were as follows: ODE ranged from 90.9% to 99.3%; CPA ranged from 75.0% to 99.3% from Weeks 108 to 144 during the double-blind phase. The percentage of subjects with HIV-1 RNA < 50 copies/mL was 100% at Week 60 for subjects who switched to ODE in the open-label extension phase.
- No subject in the ODE group had emergent resistance to study drug, compared with 1 subject in the CPA group. No subjects developed treatment-emergent drug resistance after Week 96 or in the open-label extension phase.
- There were statistically significant differences favoring ODE over CPA at Week 120 for hip and spine BMD as shown by percentage changes from baseline in hip BMD ($p < 0.001$) and spine BMD ($p < 0.001$) during the double-blind phase.
- In both treatment groups, study drug was well tolerated, with low rates of SAEs and AEs leading to study drug discontinuation during the double-blind phase and open-label extension phase.

- CD4 cell counts were maintained in both groups during the double-blind phase (mean changes from baseline at Week 96: ODE 12 cells/μL; CPA 16 cells/μL) and open-label extension phase (mean changes from baseline at Week 60: subjects who switched to ODE: 75 cells/μL).
- There were increases from baseline in fasting values for total cholesterol, direct LDL cholesterol, and triglycerides in the ODE group, and no clinically relevant changes from baseline in fasting values for HDL cholesterol, total cholesterol to HDL ratio or glucose in either treatment group during the double-blind phase and open-label extension phase.