FINAL SYNOPTIC CLINICAL STUDY REPORT

Study Title:	A Phase 3b, Randomized, Double-Blind Study to Evaluate Switching from a Regimen Consisting of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) Fixed Dose Combination (FDC) to Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) FDC in Virologically-Suppressed, HIV-1 Infected Subjects
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-366-1160
Phase of Development:	Phase 3b
IND No.:	123098
EudraCT No.:	2014-004779-21
ClinicalTrials.gov Identifier:	NCT02345226
Study Start Date:	26 January 2015 (First Subject Screened)
Study End Date:	29 June 2016 (Last Subject Last Observation for the Primary Endpoint) 11 January 2019 (Last Subject Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Edwin DeJesus, MD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: Sean Collins, MD, MS Telephone: PPD Fax: PPD
Report Date:	11 September 2019
Previous Report Date(s):	18 August 2016 (Interim Week 48 Clinical Study Report) 17 October 2017 (Interim Week 96 Clinical Study Report)

STUDY SYNOPSIS

Study GS-US-366-1160
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3b, Randomized, Double-Blind Study to Evaluate Switching from a Regimen Consisting of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) Fixed Dose Combination (FDC) to Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) FDC in Virologically-Suppressed, HIV-1 Infected Subjects

Investigators: This is a multicenter study.

Study Centers: Subjects were enrolled at 120 sites in 8 countries: 85 sites in the United States (US), 9 in Germany, 8 in Canada, 6 in Spain, 4 in the United Kingdom (UK), 3 in France, 3 in Switzerland, and 2 in Belgium

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, and White KL. No Emergent Resistance in HIV-1 Virologically-Suppressed Subjects Who Switched to RPV/FTC/TAF [Poster 1381]. ID Week 2017 4–8 October; San Diego, California.

E DeJesus, M Ramgopal, G Crofoot, P Ruane, A LaMarca. J-M Molina 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.

DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, Mills A, et al. Switching from efavirenz, emtricitabine, and 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)30032-2 The Lancet HIV 2017:1 9.

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, Washington.

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)

29 June 2016 (Last Subject Last Observation for the Primary Endpoint)

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

Phase of Development: Phase 3b

Objectives:

Study GS-US-366-1160 was conducted to evaluate the efficacy, safety, and tolerability of switching to emtricitabine (FTC)/rilpivirine (RPV)/tenofovir alafenamide (TAF) fixed-dose combination (FDC) tablet (FTC/RPV/TAF FDC; Odefsey® [ODE]) from efavirenz (EFV)/FTC/tenofovir disoproxil fumarate (TDF) FDC tablet (EFV/FTC/TDF FDC; Atripla® [ATR]) 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 ATR in virologically suppressed HIV-infected subjects as determined by maintaining HIV-1 RNA < 50 copies/mL at Week 48 (using the US Food and Drug Administration [FDA]-defined snapshot algorithm)

The secondary objectives of this study were as follows:

- To evaluate the safety and tolerability of the 2 treatment groups through Week 48
- To evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Week 96
- To determine the safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) as assessed by dual energy X-ray absorptiometry (DXA) at Weeks 48 and 96
- To evaluate the tolerability of the 2 treatment groups as determined by the change from baseline in the HIV Symptoms Index Questionnaire at Weeks 48 and 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 ATR in HIV-infected subjects who have been virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen of ATR 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 ATR once daily

Treatment Group 2: ATR (EFV/FTC/TDF 600/200/300 mg) FDC tablet once daily + placebo-to-match ODE once daily

Following screening and baseline/Day 1, subjects returned for study visits at Weeks 4, 8, 12, and then every 12 weeks. Subjects were treated for at least 96 weeks. After the last subject completed the Week 96 visit and 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 for oral once daily use, 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 800 subjects (400 in each treatment group)
Analyzed: (by analysis set) (Tables 15.8.5.1 and 15.8.5.2)

Subjects, n (%)	ODE	ATR	Total
All Randomized Analysis Set	440	441	881
Safety Analysis Set	438 (99.5%)	437 (99.1%)	875 (99.3%)
Full Analysis Set (FAS)	438 (99.5%)	437 (99.1%)	875 (99.3%)
Hip DXA Analysis Set	388 (88.2%)	399 (90.5%)	787 (89.3%)
Spine DXA Analysis Set	394 (89.5%)	400 (90.7%)	794 (90.1%)
All FTC/RPV/TAF Analysis Set	438	21[a]	459
All FTC/RPV/TAF Hip DXA Analysis Set	394 (90.0%)	19 (90.5%)	413 (90.0%)
All FTC/RPV/TAF Spine DXA Analysis Set	400 (91.3%)	19 (90.5%)	419 (91.3%)

For the double-blind phase the denominator for percentages was based on the number of subjects in the All Randomized Analysis Set.
For the All FTC/RPV/TAF Analysis Set, the denominator for the percentages was based on the number of subjects in the All FTC/RPV/TAF Analysis Set.
[a] These subjects switched from ATR 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 ATR for ≥ 6 consecutive months prior to screening, with no documented resistance to any of the study agents at any time in the past, 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 (1 × FTC/RPV/TAF 200/25/25 mg FDC tablet) administered orally, with food, once daily at approximately the same time each day + placebo (1 × placebo-to-match ATR tablet) administered orally, on an empty stomach, once daily at bedtime.

ODE Batch Numbers: EF1401B2, EF1403B1, EF1505B1, EF1506B1, EF1513B1, EF1701B1

Placebo-to-Match ATR Batch Numbers: AA1201B1, AA1501B1, AA1601B1

Reference Therapy, Dose, Mode of Administration, Batch No.: ATR (1 × EFV/FTC/TDF 600/200/300 mg FDC tablet) administered orally, on an empty stomach, once daily at bedtime + placebo (1 × placebo-to-match ODE tablet) administered orally, with food, once daily at approximately the same time each day.

ATR Batch Numbers: AA1202B1, AA1502B1, K301437, AA1602B1, AA1701B1

Placebo-to-Match ODE Batch Numbers: EF1406B1, EF1504B1, EF1514B1, EF1516B1, EF1601B1, EF1702B1

Criteria for Evaluation:

Efficacy: The primary and secondary efficacy endpoints were presented in the GS-US-366-1160 Interim Weeks 48 and 96 Clinical Study Reports (CSRs).

Efficacy endpoints evaluated for the 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 cell count and 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 were 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.

For the double-blind phase analysis, the difference in proportion of subjects with HIV-1 RNA < 50 copies/mL and its 95% confidence interval (CI) between randomized treatment groups was calculated based on an unconditional exact method using 2 inverted 1-sided tests. For M = F analysis, results were plotted by treatment group for subjects in the FAS.

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% 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 974 subjects were screened, and 881 subjects were randomized. Of these, 875 subjects received at least 1 dose of study drug and were included in the Safety Analysis Set and FAS (ODE 438 subjects; ATR 437 subjects). Of the 875 subjects treated with study drug, 46 subjects received at least 1 dose of open-label ODE (ODE 25 subjects; subjects who switched from ATR to ODE: 21 subjects) during the open-label extension phase (Table 15.8.1.1).

Double-Blind Phase

Of the 875 subjects treated with study drug, 17.0% (149 subjects) prematurely discontinued study drug treatment in the double-blind phase (ODE 16.4%, 72 subjects; ATR 17.6%, 77 subjects). The most common reasons subjects prematurely discontinued study drug were withdrawal of consent (ODE 8.2%, 36 subjects; ATR 8.5%, 37 subjects), AE (ODE 3.2%, 14 subjects; ATR 2.7%, 12 subjects), and lost to follow-up (ODE 2.1%, 9 subjects; ATR 3.4%, 15 subjects); other reasons were each recorded for ≤ 1% of subjects overall.

The discontinuation profile was similar in both treatment groups. Through the double-blind phase, 726 subjects (83.0% of 875 treated subjects) completed study drug treatment (ODE 83.6%, 366 subjects; ATR 82.4%, 360 subjects), and 741 subjects (84.7% of 875 treated subjects) completed the double-blind phase (ODE 84.7%, 371 subjects; ATR 84.7%, 370 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 49 years (range: 19 to 76 years). Most subjects were male (87.2%), white (66.6%) or black (27.2%), and not Hispanic or Latino (81.9%). The median (first quartile [Q1], third quartile [Q3]) body mass index at baseline was 26.0 (23.6, 29.0) 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, 98.5% of subjects in the Safety Analysis Set had baseline HIV-1 RNA < 50 copies/mL. The median (Q1, Q3) baseline CD4 count was 667 (505, 852) cells/µL, and 75.9% of subjects had CD4 count ≥ 500 cells/µL. The most common HIV risk factor category was homosexual sex (72.1%); 25.4% of subjects reported heterosexual sex as the mode of infection. Most subjects (92.6%) 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 114.0 [31.88] mL/min; ATR 113.2 [32.28] mL/min) (Table 15.8.3.3).

Open-Label Extension Phase

Of the 875 subjects treated with study drug, 5.3% (46 subjects) entered the open-label extension phase and were treated (ODE 5.7%, 25/438 subjects; subjects who switched from ATR to ODE: 4.8%, 21/437 subjects).Through the open-label extension phase, 45 subjects (97.8% of 46 subjects) completed study drug treatment (ODE 100%, 25/25 subjects; subjects who switched from ATR to ODE: 95.2%, 20/21 subjects), and 45 subjects (97.8% of 46 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-366-1160 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 87.2%; ATR 87.9%. 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%; ATR 100.0%. 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 96.4% to 99.5%; ATR ranged from 96.9% to 98.9% from Weeks 108 to 144. The differences in response rate between treatment groups at Week 96 were as follows: M = F: −0.7%, 95% CI: −5.1% to 3.8%;
M = E: −0.3%, 95% CI: −1.5% to 0.8%. For the M = E analysis, the differences in response rate between treatment groups ranged from 0.5%, 95% CI: −1.0% to 2.2% at Week 108 to −0.4%, 95% CI: −15.5% to 13.3% at Week 144 (Tables 15.9.3.1.1 and 15.9.3.1.2).

Mean [SD] baseline CD4 cell counts and CD4% were similar between treatment groups (ODE 711 [292.3] cells/μL and 36.3 [9.50]%, respectively; ATR 688 [263.5] cells/μL and 36.1 [8.75]%, respectively). CD4 cell counts and CD4% were maintained in both groups; mean [SD] changes from baseline at Week 96 (FAS) were as follows: ODE 13 [199.8] cells/μL and 0.1 [4.37]%, respectively; ATR 6 [153.2] cells/μL and 1.0 [3.83]%, respectively (difference in least-squares mean: 7 cells/μL, 95% CI: −19 to 32 cells/μL and −0.9%, 95% CI −1.5 to 0.3%, respectively) (Tables 15.9.2.2.1 and 15.9.3.3.1).

Efficacy was maintained after Week 96, as the mean [SD] CD4 cell counts and CD4% changes from baseline were as follows: ODE ranged from 17 [175.4] cells/μL to 34 [205.5] cells/μL (−0.4 [4.41]% to −0.2[4.65]%); ATR ranged from 24 [160.7] cells/μL to 29 [164.5] cells/μL (0.5 [5.16]% to 1.0 [4.14]%) from Week 108 to 132 (Tables 15.9.2.2.1 and 15.9.3.3.1). The interpretation of results obtained after Week 132 was limited since only 15 subjects in the ODE treatment group and 14 subjects in the ATR 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).

Mean [SD] baseline CD4 cell counts and CD4% in subjects who switched from ATR to ODE were: 708 [187.1] cells/μL and 33.9 [7.36]%, respectively. CD4 cell counts and CD4% were maintained in subjects who switched from ATR to ODE in the open-label extension phase: mean changes from baseline at Week 48 (All FTC/RPV/TAF Analysis Set) were as follows:

−11 [169.9] cells/μL and 1.2 [3.52]%, respectively (Tables 15.9.2.2.2 and 15.9.3.3.2). Only 3 subjects had data at Week 60 and no subjects had data after Week 60.

Virology Resistance Data:

Double-Blind Phase

Subjects receiving ODE

Of the 438 treated subjects from the ODE group, 10 subjects were included in the resistance analysis population through end of study (2.3%; 10 of 438 subjects). Of these 10 subjects, 9 had post-baseline genotypic and phenotypic data for PR/RT available. Seven of the 10 subjects in the ODE group resuppressed to HIV-1 RNA < 50 copies/mL and no subjects had emergent resistance to study drug.

Subjects receiving ATR

Of the 437 treated subjects from the ATR group, 4 subjects were included in the resistance analysis population through end of study (0.9%; 4 of 437 subjects). Of these 4 subjects, 4 had post-baseline genotypic and phenotypic data for PR/RT available. Prior to Week 96, 2 subjects had emergent resistance to study drugs. Subject PPD developed genotypic and phenotypic resistance to both emtricitabine (FTC; M184V; FTC fold change (FC) >79) and efavirenz (EFV; V106I/L and Y188L; EFV FC >109) at Week 24, but remained susceptible to tenofovir (TFV). Subject PPD developed genotypic and phenotypic resistance to EFV (K101K/E,

K103N, and P225P/H; EFV FC = 12.3) at Early Study Drug Discontinuation but remained susceptible to both FTC and TFV. No subjects in the ATR resistance analysis population (RAP) group resuppressed to HIV-1 RNA < 50 copies/mL and none developed treatment-emergent drug resistance after Week 96.

Open-Label Extension Phase

Of the 21 treated subjects from the ATR to ODE group, 1 subject was included in the resistance analysis population through end of study (4.8%; 1 of 21 subjects). This subject did not have post-baseline genotypic and phenotypic data for PR/RT available and did not resuppress to HIV-1 RNA < 50 copies/mL.

Pharmacokinetics Results:

No PK analyses were performed for this report. All intensive PK analyses and summary statistics were included in the GS-US-366-1160 Interim Week 48 CSR.

Safety Results:

Double-Blind Phase

In subjects in the Safety Analysis Set who switched from ATR to ODE, ODE was generally well tolerated through a median of 117.4 weeks of exposure (Table 15.11.1.1), as evidenced by the infrequent discontinuations due to AEs (Table 15.11.2.1.1) and only 2 subjects experiencing study drug-related serious adverse events (SAEs) (Table 15.11.4.3). In subjects in the Safety Analysis Set who continued on ATR, study drug was generally well tolerated through a median of 117.4 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 92.0%, 403 of 438 subjects; ATR 89.5%, 391 of 437 subjects). Three treatment-emergent deaths occurred during the double-blind phase, all in the ODE group: 1 subject died as a result of sepsis, 1 subject died as a result of pneumonia due to lung cancer, and 1 subject died as a result of cocaine and meth overdose (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.

The incidence of SAEs was low in the double-blind phase (ODE 12.3%, 54 of 438 subjects; ATR 10.3%, 45 of 437 subjects); only 2 subjects in the ATR group experienced SAEs that were considered related to study drug. These events were atrial fibrillation and Fanconi syndrome acquired (Tables 15.11.4.1 and 15.11.4.3). There were no SAEs that were considered related to study drug in the ODE group. The percentage of subjects that had any AE considered related to study drug was similar between groups (ODE 14.2%, 62 subjects; ATR 13.7%, 60 subjects) (Table 15.11.2.3.1.1). The incidence of Grade 3 or Grade 4 AEs was low (ODE 12.6%, 55 subjects; ATR 10.1%, 44 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 3.2%, 14 subjects; ATR 2.7%, 12 subjects). The only AEs that led to study drug discontinuation that were reported for more than 1 subject in either group were fatigue and cough in the ODE group (2 subjects each) and insomnia in the ATR group (2 subjects) (Table 15.11.5.1). Fourteen subjects had study drug-related AEs leading to study drug discontinuation (ODE 1.1%, 5 subjects; ATR 2.1%, 9 subjects) (Listing 16.2.7.5). These events occurred prior to the Week 96 data cut and have 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: upper respiratory tract infection (16.9%, 74 of 438 subjects), nasopharyngitis (11.6%, 51 subjects), and cough (10.3%, 45 subjects) (Tables 15.11.2.1.3 and 15.11.2.1.5)
- ATR: upper respiratory tract infection (16.0%, 70 of 437 subjects), diarrhea (10.8%, 47 subjects), and arthralgia (9.6%, 42 subjects) (Tables 15.11.2.1.3 and 15.11.2.1.5)

Bone Safety

There were increases from baseline through Week 120 in mean [SD] BMD at the hip and spine in subjects who switched to ODE, compared with minimal changes in both for subjects who remained on ATR ($p < 0.001$ for the difference between groups for both hip and spine) (Tables 15.11.2.4.2.1 and 15.11.2.4.2.2).

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

- Hip: ODE 1.805% [3.4728%]; ATR −0.647% [3.3782%] (Table 15.11.2.4.2.1)
- Spine: ODE 1.925% [3.9009%]; ATR 0.251% [3.4709%] (Table 15.11.2.4.2.2)

Renal Safety

Three subjects in the ATR group had renal SAEs (2 subjects had SAEs of acute kidney injury and 1 subject had SAEs of acute kidney injury, acquired Fanconi syndrome, and ureterolithiasis which led to study drug discontinuation) (Table 15.11.4.1 and Listing 16.2.7.3). The acquired Fanconi syndrome was considered related to study drug (Table 15.11.4.3 and Listing 16.2.7.3). One subject (ODE group) discontinued study drug due to decreased glomerular filtration rate, considered by the investigator as related to study drug (Listing 16.2.7.5).

For serum creatinine, median baseline values were the same in the 2 treatment groups. An increase in serum creatinine in the ODE group was observed at Week 4 and was stable from Week 12 through Week 132. Week 144 values were also similar but the number of evaluable subjects reduced to 22 in the ODE group and 23 in the ATR group (median Week 132 values: ODE 0.99 mg/dL; ATR 0.98 mg/dL). The difference between groups in the change from baseline in serum creatinine was statistically significant at all time points from Week 4 through Week 120 ($p < 0.001$ at each time point) (Table 15.11.2.4.4.1). The increase in creatinine is consistent with the known effects of RPV on tubular secretion of creatinine and does not represent a true change in renal function.

For $eGFR_{CG}$, median baseline values were similar in the 2 treatment groups. A decrease in $eGFR_{CG}$ was observed in the ODE group at Week 4 and was stable from Week 12 through Week 96 (median Week 96 values: ODE 105.4 mL/min; ATR 106.4 mL/min; mean Week 96 values: ODE 109.5 mL/min; ATR 111.8 mL/min). The difference between groups in the change from baseline in $eGFR_{CG}$ was statistically significant at all time points from Week 4 through Week 96 ($p < 0.001$ at all time points from Week 4 through Week 84 and $p = 0.004$ at Week 96) (Table 15.11.2.4.5.1). The decrease in $eGFR_{CG}$ in the ODE group is consistent with the known effects of RPV on tubular secretion of creatinine, has no effect on actual glomerular filtration, does not represent a true change in renal function, and is not considered clinically relevant.

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.

Most subjects had at least 1 laboratory abnormality (ODE 89.5%, 391 subjects; ATR 89.2%, 387 subjects). Most reported abnormalities were Grade 1 or Grade 2 (Table 15.11.6.4.1.1). The percentages of subjects with Grade 3 or Grade 4 abnormalities was similar between groups (ODE 16.9%, ATR 15.2%) (Table 15.11.6.4.2.1).

Metabolic Laboratory Parameters

There were decreases from baseline in fasting values of total cholesterol and high-density lipoprotein (HDL) cholesterol in the ODE group, while these parameters had little change or slight decreases in the ATR group at Weeks 24, 48, 72, and 96. These changes may have been a result of discontinuing treatment with EFV (a component of ATR), which is associated with increases in both total cholesterol and HDL cholesterol. The total cholesterol to HDL ratio was similar between groups through Week 120. Decreases from baseline in fasting low-density lipoprotein (LDL) and triglycerides were similar between groups at Week 96 (Tables 15.11.6.3.1.1, 15.11.6.3.2.1, 15.11.6.3.3.1, 15.11.6.3.4.1, and 15.11.6.3.5.1). There were no clinically relevant changes from baseline in median fasting values for total cholesterol, LDL or glucose in either treatment group (Tables 15.11.6.3.1.1, 15.11.6.3.2.1, and 15.11.6.3.6.1).

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

- LDL: ODE −2 (−20, 15) mg/dL; ATR 0 (−16, 12) mg/dL ($p = 0.49$) (Table 15.11.6.3.2.1)
- HDL: ODE −4 (−10, 1) mg/dL; ATR −1 (−5, 5) mg/dL ($p < 0.001$) (Table 15.11.6.3.3.1)
- Total cholesterol to HDL ratio: ODE 0.1 (−0.4, 0.6): ATR 0.0 (−0.4, 0.3) ($p = 0.007$) (Table 15.11.6.3.4.1)
- Triglycerides: ODE −5 (−36, 29) mg/dL, ATR 4 (−27, 32) mg/dL ($p = 0.041$) (Table 15.11.6.3.5.1)

ECG Abnormalities

Clinically significant ECG findings were reported for 5 subjects in the ODE group and 6 subjects in the ATR group (Listing 16.2.8.5). Adverse events related to ECGs were reported in 5 subjects in the ODE group and 2 subjects in the ATR group (Table 15.11.2.1.3); none resulted in study drug discontinuation (Table 15.11.5.1). Two AEs were considered related to study drug (ODE: ST segment elevation; ATR: QT prolonged) (Table 15.11.2.3.1.1).

Body Weight and Vital Signs

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

There were no clinically relevant findings in vital signs (Tables 15.11.7.1.1.1, 15.11.7.1.2.1, 15.11.7.1.3.1, 15.11.7.1.4.1, and 15.11.7.1.5.1).

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

In subjects in the All FTC/RPV/TAF Analysis Set who switched from ATR to ODE in the open-label extension phase, study drug was generally well tolerated through a median of 44.9 weeks of exposure (Table 15.11.1.2).

Adverse Events

No treatment-emergent deaths or AEs leading to study drug discontinuation occurred in subjects who switched from ATR to ODE in the open-label extension phase (Tables 15.11.2.1.2 and 15.11.5.2). One subject who switched from ATR to ODE in the open-label extension phase experienced an SAE (diarrhea infectious), which was considered unrelated to study drug (Tables 15.11.4.2 and 15.11.4.4).

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 only events occurring in more than one person, in subjects who switched from ATR to ODE in the open-label extension phase, were diarrhea, syphilis, cough, and eczema (these events occurred in 2 subjects each) (Tables 15.11.2.1.4 and 15.11.2.1.6).

Bone Safety

Few subjects in the hip or spine DXA sub-study 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 0.12 (0.07, 0.19) mg/dL (Table 15.11.2.4.4.2). At Week 60 overall median (Q1, Q3) changes from baseline in $eGFR_{CG}$ were −9.6 (−15.3, −6.9) mL/min in subjects who switched to ODE in the open-label extension phase (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.

Around half of the subjects who switched from ATR to ODE in the open-label extension phase had at least 1 laboratory abnormality: 57.1%, 12 of 21 subjects. Most reported abnormalities were Grade 1 or Grade 2 (Table 15.11.6.4.1.2). There were no Grade 3 abnormalities; 4.8%, 1 of 21 subjects had Grade 4 abnormalities (Table 15.11.6.4.2.2).

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline in fasting values of total cholesterol, direct LDL, HDL, triglycerides or glucose at Week 48 in subjects who switched from ATR to ODE in the open-label extension phase (Tables 15.11.6.3.1.2, 15.11.6.3.2.2, 15.11.6.3.3.2, 15.11.6.3.5.2, and 15.11.6.3.6.2). There were no clinically relevant changes from baseline in fasting total cholesterol to HDL cholesterol ratio (Table 15.11.6.3.4.2).

ECG Abnormalities

No AEs related to ECGs were reported in the subjects who switched from ATR to ODE in the open-label extension phase (Table 15.11.2.1.4).

Body Weight and Vital Signs

There were no clinically relevant findings in body weight and vital signs (Tables 15.11.7.2.2, 15.11.7.1.1.2, 15.11.7.1.2.2, 15.11.7.1.3.2, 15.11.7.1.4.2, and 15.11.7.1.5.2).

CONCLUSIONS: Follow-up of subjects through the end of study 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 96.4% to 99.5%; ATR ranged from 96.9% to 98.9% 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 in subjects who switched from ATR to ODE during the open-label extension phase. There were no subjects after Week 60.
- No subject in the ODE group had emergent resistance to study drug, compared with 2 subjects in the ATR 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 ATR through 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 and beyond (mean changes from baseline at Week 96: ODE 13 cells/μL; ATR 6 cells/μL). CD4 counts were also maintained in subjects who switched from ATR to ODE in the open-label phase (mean changes from baseline at Week 48: −11 cells/μL). For those subjects who switched, the interpretation of results at Week 60 is limited as there were only 3 subjects and there were no subjects after Week 60.
- There were decreases from baseline in the fasting total cholesterol and HDL cholesterol in the ODE group, and no clinically relevant changes from baseline in median fasting values for total cholesterol to HDL ratio, LDL cholesterol, triglycerides, or glucose in either treatment group during the double-blind phase and open-label extension phase